The American Journal of Cardiology®

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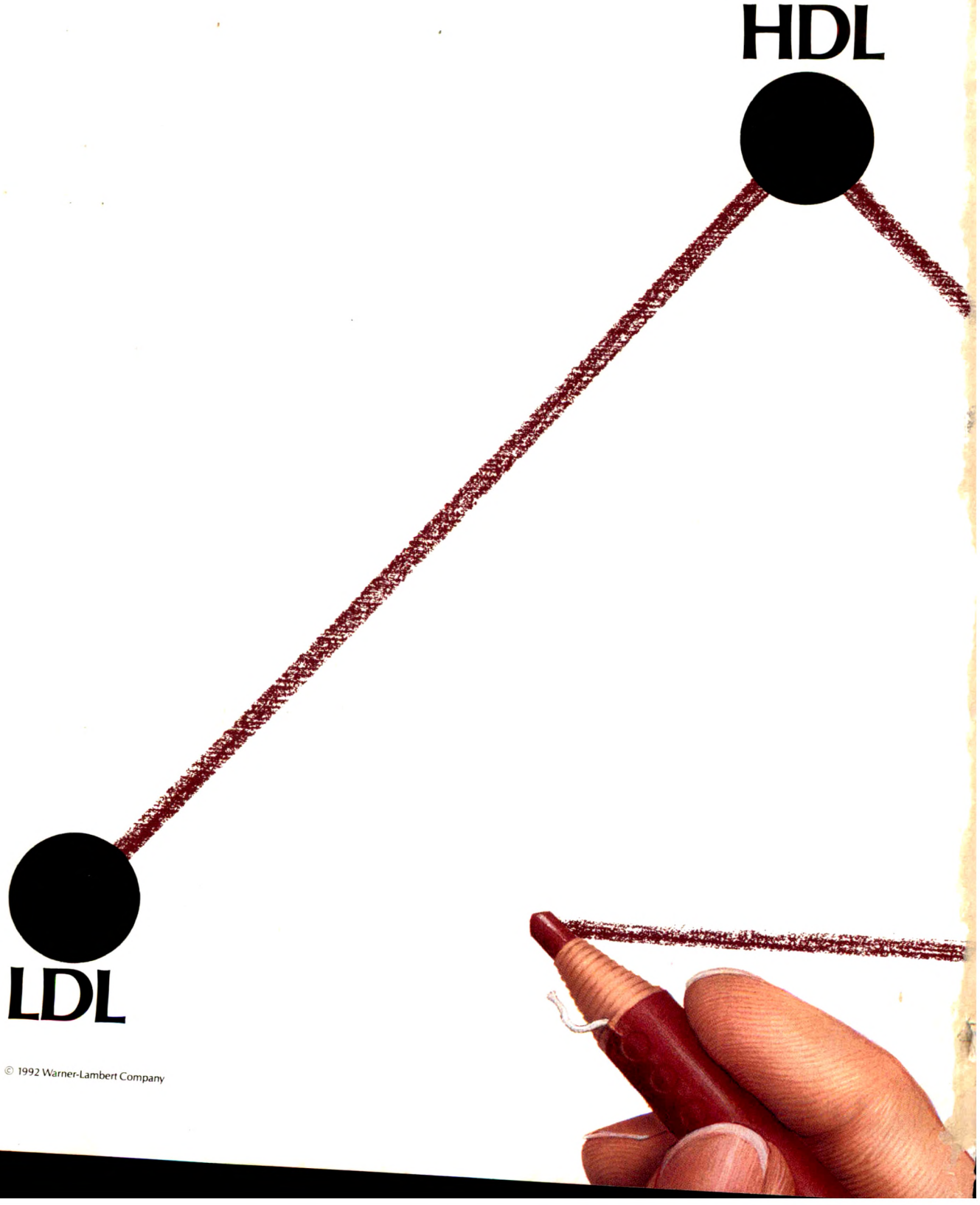
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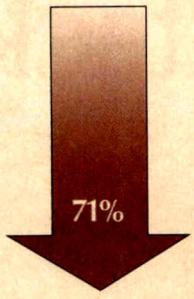


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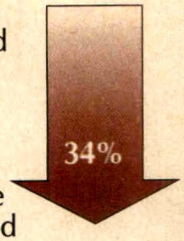
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To reduce the risk of heart attack, don't overlook coexisting low HDL, high triglycerides, and high LDL. A recently published analysis of data from the 5-year primary prevention Helsinki Heart Study (HHS) shows why:

LOPID reduced the incidence of heart attack* 71%



—in a high-risk subgroup of patients with this triad of lipid disorders. While the overall reduction in the HHS was 34%, the greatest reduction was achieved among these LOPID patients with baseline triglycerides >200 mg/dL and baseline LDL/HDL ratio >5 (n = 154).[†1]



LOPID® BID
(gemfibrozil) 600-mg Tablets

TREATS THE ENTIRE TRIAD DRAMATICALLY REDUCES HEART ATTACK

LOPID is indicated for reducing the risk of developing coronary heart disease **only** in type IIb patients without history or symptoms of existing coronary heart disease, who have had an inadequate response to weight loss, diet, exercise, and other pharmacologic agents (such as bile acid sequestrants and nicotinic acid) and who have had the following triad of lipid abnormalities: low HDL in addition to elevated LDL and triglycerides. LOPID is not indicated for the treatment of patients with low HDL as their only lipid abnormality.

Contraindicated in patients with hepatic or severe renal dysfunction, including primary biliary cirrhosis, preexisting gallbladder disease, or hypersensitivity to gemfibrozil. LOPID may increase cholesterol secretion into the bile, leading to cholelithiasis. Caution should be exercised when anticoagulants are given in conjunction with LOPID.

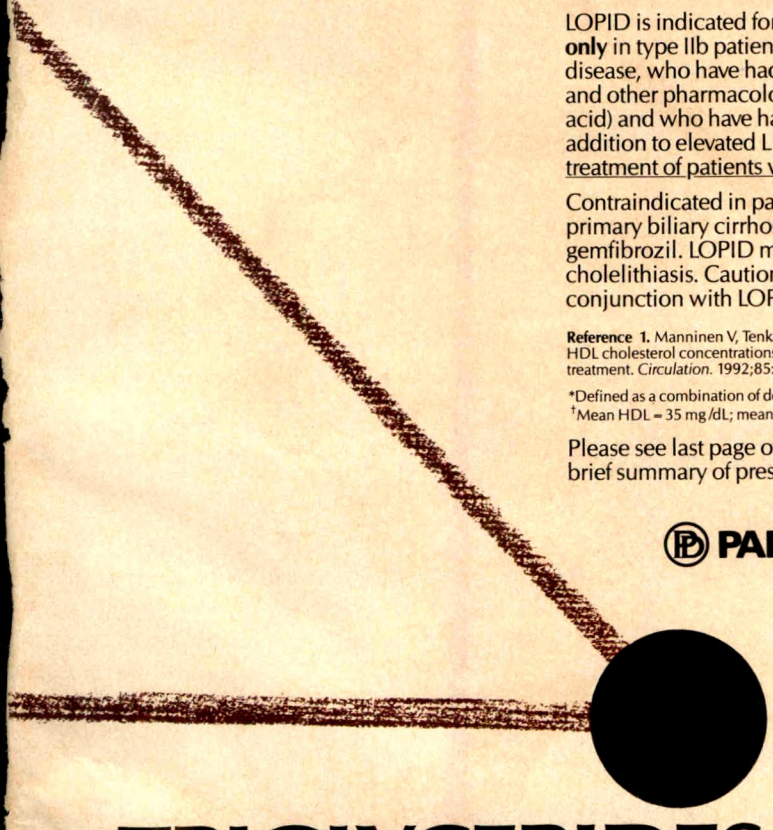
Reference 1. Manninen V, Tenkanen L, Koskinen P, et al. Joint effects of serum triglyceride and LDL cholesterol and HDL cholesterol concentrations on coronary heart disease risk in the Helsinki Heart Study: implications for treatment. *Circulation.* 1992;85:37-45.

*Defined as a combination of definite coronary death and/or definite myocardial infarction.
†Mean HDL = 35 mg/dL; mean LDL = 208 mg/dL; $P = .005$; 95% CI 21.2 to 118.6.

Please see last page of this advertisement for warnings, contraindications, and brief summary of prescribing information.

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BOOTS PHARMACEUTICALS



TRIGLYCERIDES



Before prescribing, please see full prescribing information. A Brief Summary follows.

CONTRAINDICATIONS

1. Hepatic or severe renal dysfunction, including primary biliary cirrhosis.
2. Preexisting gallbladder disease (see WARNINGS).
3. Hypersensitivity to gemfibrozil.

WARNINGS

1. Because of chemical, pharmacological, and clinical similarities between gemfibrozil and clofibrate, the adverse findings with clofibrate in two large clinical studies may also apply to gemfibrozil. In the first of those studies, the Coronary Drug Project, 1000 subjects with previous myocardial infarction were treated for five years with clofibrate. There was no difference in mortality between the clofibrate-treated subjects and 3000 placebo-treated subjects, but twice as many clofibrate-treated subjects developed cholelithiasis and cholecystitis requiring surgery. In the other study, conducted by the World Health Organization (WHO), 5000 subjects without known coronary heart disease were treated with clofibrate for five years and followed one year beyond. There was a statistically significant, 44%, higher age-adjusted total mortality in the clofibrate-treated than in a comparable placebo-treated control group during the trial period. The excess mortality was due to a 33% increase in noncardiovascular causes, including malignancy, post-cholecystectomy complications, and pancreatitis. The higher risk of clofibrate-treated subjects for gallbladder disease was confirmed.

Because of the more limited size of the Helsinki Heart Study, the observed difference in mortality from any cause between the Lopid and placebo group is not statistically significantly different from the 29% excess mortality reported in the clofibrate group in the separate WHO study at the 9 year follow-up (see CLINICAL PHARMACOLOGY). Noncoronary heart disease related mortality showed an excess in the group originally randomized to Lopid primarily due to cancer deaths observed during the open-label extension.

During the 5 year primary prevention component of the Helsinki Heart Study mortality from any cause was 44 (2.2%) in the Lopid group and 43 (2.1%) in the placebo group; including the 3.5 year follow-up period since the trial was completed, cumulative mortality from any cause was 101 (4.9%) in the Lopid group and 83 (4.1%) in the group originally randomized to placebo (hazard ratio 1.20 in favor of placebo). Because of the more limited size of the Helsinki Heart Study, the observed difference in mortality from any cause between the Lopid and placebo groups at year-5 or at year-8.5 is not statistically significantly different from the 29% excess mortality reported in the clofibrate group in the separate WHO study at the 9 year follow-up. Noncoronary heart disease related mortality showed an excess in the group originally randomized to Lopid at the 8.5 year follow-up (65 Lopid versus 45 placebo noncoronary deaths).

The incidence of cancer (excluding basal cell carcinoma) discovered during the trial and in the 3.5 years after the trial was completed was 51 (2.5%) in both originally randomized groups. In addition, there were 16 basal cell carcinomas in the group originally randomized to Lopid and 9 in the group originally randomized to placebo ($p = 0.22$). There were 30 (1.5%) deaths attributed to cancer in the group originally randomized to Lopid and 18 (0.9%) in the group originally randomized to placebo ($p = 0.11$). Adverse outcomes, including coronary events, were higher in gemfibrozil patients in a corresponding study in men with a history of known or suspected coronary heart disease in the secondary prevention component of the Helsinki Heart Study. (See CLINICAL PHARMACOLOGY.)

2. A gallstone prevalence substudy of 450 Helsinki Heart Study participants showed a trend toward a greater prevalence of gallstones during the study within the Lopid treatment group (7.5% vs 4.9% for the placebo group, a 55% excess for the gemfibrozil group). A trend toward a greater incidence of gallbladder surgery was observed for the Lopid group (17 vs 11 subjects, a 54% excess). This result did not differ statistically from the increased incidence of cholecystectomy observed in the WHO study in the group treated with clofibrate. Both clofibrate and gemfibrozil may increase cholesterol excretion into the bile leading to cholelithiasis. If cholelithiasis is suspected, gallbladder studies are indicated. Lopid therapy should be discontinued if gallstones are found.

3. Since a reduction of mortality from coronary heart disease has not been demonstrated and because liver and interstitial cell testicular tumors were increased in rats, Lopid should be administered only to those patients described in the INDICATIONS AND USAGE section. If a significant serum lipid response is not obtained, Lopid should be discontinued.

4. Concomitant Anticoagulants – Caution should be exercised when anticoagulants are given in conjunction with Lopid. The dosage of the anticoagulant should be reduced to maintain the prothrombin time at the desired level to prevent bleeding complications. Frequent prothrombin determinations are advisable until it has been definitely determined that the prothrombin level has stabilized.

5. Concomitant therapy with Lopid and Mevacor® (lovastatin) has been associated with rhabdomyolysis, markedly elevated creatine kinase (CK) levels and myoglobinuria, leading in a high proportion of cases to acute renal failure. IN VIRTUALLY ALL PATIENTS WHO HAVE HAD AN UNSATISFACTORY LIPID RESPONSE TO EITHER DRUG ALONE, ANY POTENTIAL LIPID BENEFIT OF COMBINED THERAPY WITH LOVASTATIN AND GEMFIBROZIL DOES NOT OUTWEIGH THE RISKS OF SEVERE MYOPATHY, RHABDOMYOLYSIS, AND ACUTE RENAL FAILURE (see Drug Interactions). The use of fibrates alone, including Lopid, may occasionally be associated with myositis. Patients receiving Lopid and complaining of muscle pain, tenderness, or weakness should have prompt medical evaluation for myositis, including serum creatine kinase level determination. If myositis is suspected or diagnosed, Lopid therapy should be withdrawn.

6. Cataracts – Subcapsular bilateral cataracts occurred in 10%, and unilateral in 6.3% of male rats treated with gemfibrozil at 10 times the human dose.

PRECAUTIONS

1. **Initial Therapy** – Laboratory studies should be done to ascertain that the lipid levels are consistently abnormal. Before instituting Lopid therapy, every attempt should be made to control serum lipids with appropriate diet, exercise, weight loss in obese patients, and control of any medical problems such as diabetes mellitus and hypothyroidism that are contributing to the lipid abnormalities.

2. **Continued Therapy** – Periodic determination of serum lipids should be obtained, and the drug withdrawn if lipid response is inadequate after 3 months of therapy.

3. **Drug Interactions** – (A) **HMG-CoA reductase inhibitors:** Rhabdomyolysis has occurred with combined gemfibrozil and lovastatin therapy. It may be seen as early as 3 weeks after initiation of combined therapy or after several months. In most subjects who have had an unsatisfactory lipid response to either drug alone, the possible benefit of combined therapy with lovastatin (or other HMG-CoA reductase inhibitors) and gemfibrozil does not outweigh the risks of severe myopathy, rhabdomyolysis, and acute renal failure. There is no assurance that periodic monitoring of creatine kinase will prevent the occurrence of severe myopathy and kidney damage.

(B) **Anticoagulants:** CAUTION SHOULD BE EXERCISED WHEN ANTICOAGULANTS ARE GIVEN IN CONJUNCTION WITH LOPID. THE DOSAGE OF THE ANTICOAGULANT SHOULD BE REDUCED TO MAINTAIN THE PROTHROMBIN TIME AT THE DESIRED LEVEL TO PREVENT BLEEDING COMPLICATIONS. FREQUENT PROTHROMBIN DETERMINATIONS ARE ADVISABLE UNTIL IT HAS BEEN DEFINITELY DETERMINED THAT THE PROTHROMBIN LEVEL HAS STABILIZED.

4. **Carcinogenesis, Mutagenesis, Impairment of Fertility** – Long-term studies have been conducted in rats at 0.2 and 2 times the human dose (based on surface area, mg/meter^2). The incidence of benign liver nodules and liver carcinomas was significantly increased in high dose male rats. The incidence of liver carcinomas increased also in low dose males, but this increase was not statistically significant ($p = 0.1$). Male rats had a dose-related and statistically significant increase of benign Leydig cell tumors. The higher dose female rats had a significant increase in the combined incidence of benign, and malignant liver neoplasms.

Long-term studies have been conducted in mice at 0.1 and 1 times the human dose (based on surface area). There were no statistically significant differences from controls in the incidence of liver tumors, but the doses tested were lower than those shown to be carcinogenic with other fibrates.

Electron microscopy studies have demonstrated a florid hepatic peroxisome proliferation following Lopid administration to the male rat. An adequate study to test for peroxisome proliferation has not been done in humans but changes in peroxisome morphology have been observed. Peroxisome proliferation has been shown to occur in humans with either of two other drugs of the fibrate class when liver biopsies were compared before and after treatment in the same individual.

Administration of approximately 0.6 and 2 times the human dose (based on surface area) to male rats for 10 weeks resulted in a dose-related decrease of fertility. Subsequent studies demonstrated that this effect was reversed after a drug-free period of about eight weeks, and it was not transmitted to the offspring.

5. **Pregnancy Category C** – Lopid has been shown to produce adverse effects in rats and rabbits at doses between 0.5 and 3 times the human dose (based on surface area) but no developmental toxicity or teratogenicity among offspring of either species. There are no adequate and well-controlled studies in pregnant women. Lopid should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Administration of Lopid to female rats at 0.6 and 2 times the human dose (based on surface area) before and throughout gestation caused a dose-related decrease in conception rate and, at the high dose, an increase in stillborns and a slight reduction in pup weight during lactation. There were also dose-related increased skeletal variations. Anophthalmia occurred, but rarely.

Lopid® (Gemfibrozil Tablets)

Administration of 0.6 and 2 times the human dose (based on surface area) of Lopid to female rats from gestation day 15 through weaning caused dose-related decreases in birth weight and suppressions of pup growth during lactation.

Administration of 1 and 3 times the human dose (based on surface area) of Lopid to female rabbits during organogenesis caused a dose-related decrease in litter size and at the high dose, an increased incidence of parietal bone variations.

6. **Nursing Mothers** – It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for tumorigenicity shown for Lopid in animal studies, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

7. **Hematologic Changes** – Mild hemoglobin, hematocrit and white blood cell decreases have been observed in occasional patients following initiation of Lopid therapy. However, these levels stabilize during long-term administration. Rarely, severe anemia, leukopenia, thrombocytopenia, and bone marrow hypoplasia have been reported. Therefore, periodic blood counts are recommended during the first 12 months of Lopid administration.

8. **Liver Function** – Abnormal liver function tests have been observed occasionally during Lopid administration, including elevations of AST (SGOT), ALT (SGPT), LDH, bilirubin, and alkaline phosphatase. These are usually reversible when Lopid is discontinued. Therefore periodic liver function studies are recommended and Lopid therapy should be terminated if abnormalities persist.

9. **Kidney Function** – There have been reports of worsening renal insufficiency upon the addition of Lopid therapy in individuals with baseline plasma creatinine > 2.0 mg/dL. In such patients, the use of alternative therapy should be considered against the risks and benefits of a lower dose of Lopid.

10. **Use in Children** – Safety and efficacy in children and adolescents have not been established.

ADVERSE REACTIONS

In the double-blind controlled phase of the primary prevention component of the Helsinki Heart Study, 2046 patients received Lopid for up to 5 years. In that study, the following adverse reactions were statistically more frequent in subjects in the Lopid group:

	LOPID (N=2046)	PLACEBO (N=2035)
	Frequency in percent of subjects	
Gastrointestinal reactions	34.2	23.8
Dyspepsia	19.6	11.9
Abdominal pain	9.8	5.6
Acute appendicitis (histologically confirmed in most cases where data were available)	1.2	0.6
Atrial fibrillation	0.7	0.1
Adverse events reported by more than 1% of subjects, but without a significant difference between groups:		
Diarrhea	7.2	6.5
Fatigue	3.8	3.5
Nausea/Vomiting	2.5	2.1
Eczema	1.9	1.2
Rash	1.7	1.3
Vertigo	1.5	1.3
Constipation	1.4	1.3
Headache	1.2	1.1

Gallbladder surgery was performed in 0.9% of Lopid and 0.5% of placebo subjects in the primary prevention component, a 64% excess, which is not statistically different from the excess of gallbladder surgery observed in the clofibrate compared to the placebo group of the WHO study. Gallbladder surgery was also performed more frequently in the Lopid group compared to placebo (1.9% vs. 0.3%, $p = 0.07$) in the secondary prevention component. A statistically significant increase in appendectomy in the gemfibrozil group was seen also in the secondary prevention component (6 on gemfibrozil vs. 0 on placebo, $p = 0.014$).

Nervous system and special senses adverse reactions were more common in the Lopid group. These included hypesthesia, paresthesias, and taste perversion. Other adverse reactions that were more common among Lopid treatment group subjects but where a causal relationship was not established include cataracts, peripheral vascular disease, and intracerebral hemorrhage.

From other studies it seems probable that Lopid is causally related to the occurrence of MUSCULOSKELETAL SYMPTOMS (see WARNINGS), and to ABNORMAL LIVER FUNCTION TESTS and HEMATOLOGIC CHANGES (see PRECAUTIONS).

Reports of viral and bacterial infections (common cold, cough, urinary tract infections) were more common in gemfibrozil treated patients in other controlled clinical trials of 805 patients. Additional adverse reactions that have been reported for gemfibrozil are listed below by system. These are categorized according to whether a causal relationship to treatment with Lopid is probable or not established:

CAUSAL RELATIONSHIP PROBABLE: *Gastrointestinal:* cholestatic jaundice; *Central Nervous System:* dizziness, somnolence, paresthesia, peripheral neuritis, decreased libido, depression, headache; *Eye:* blurred vision; *Genitourinary:* impotence; *Musculoskeletal:* myopathy, myasthenia, myalgia, painful extremities, arthralgia, synovitis, rhabdomyolysis (see WARNINGS and Drug Interactions under PRECAUTIONS); *Clinical Laboratory:* increased creatine phosphokinase, increased bilirubin, increased liver transaminases (AST [SGOT], ALT [SGPT]), increased alkaline phosphatase; *Hematopoietic:* anemia, leukopenia, bone marrow hypoplasia, eosinophilia; *Immunologic:* angioedema, laryngeal edema, urticaria; *Integumentary:* exfoliative dermatitis, rash, dermatitis, pruritus.

CAUSAL RELATIONSHIP NOT ESTABLISHED: *General:* weight loss; *Cardiac:* extrasystoles; *Gastrointestinal:* pancreatitis, hepatoma, colitis; *Central Nervous System:* confusion, convulsions, syncope; *Eye:* retinal edema; *Genitourinary:* decreased male fertility, renal dysfunction; *Clinical Laboratory:* positive antinuclear antibody; *Hematopoietic:* thrombocytopenia; *Immunologic:* anaphylaxis, Lupus-like syndrome, vasculitis; *Integumentary:* alopecia.

DOSAGE AND ADMINISTRATION

The recommended dose for adults is 1200 mg administered in two divided doses 30 minutes before the morning and evening meal.

OVERDOSAGE

While there has been no reported case of overdosage, symptomatic supportive measures should be taken should it occur.

HOW SUPPLIED

Lopid (Tablet 737), white, elliptical, film-coated, scored tablets, each containing 600 mg gemfibrozil, are available as follows:

N 0071-0737-20 Bottles of 60
N 0071-0737-30 Bottles of 500
N 0071-0737-40 Unit dose packages of 100 (10 strips of 10 tablets each)
Parcode® No. 737

Storage: Store below 30° C (86° F).

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Revised April 1992

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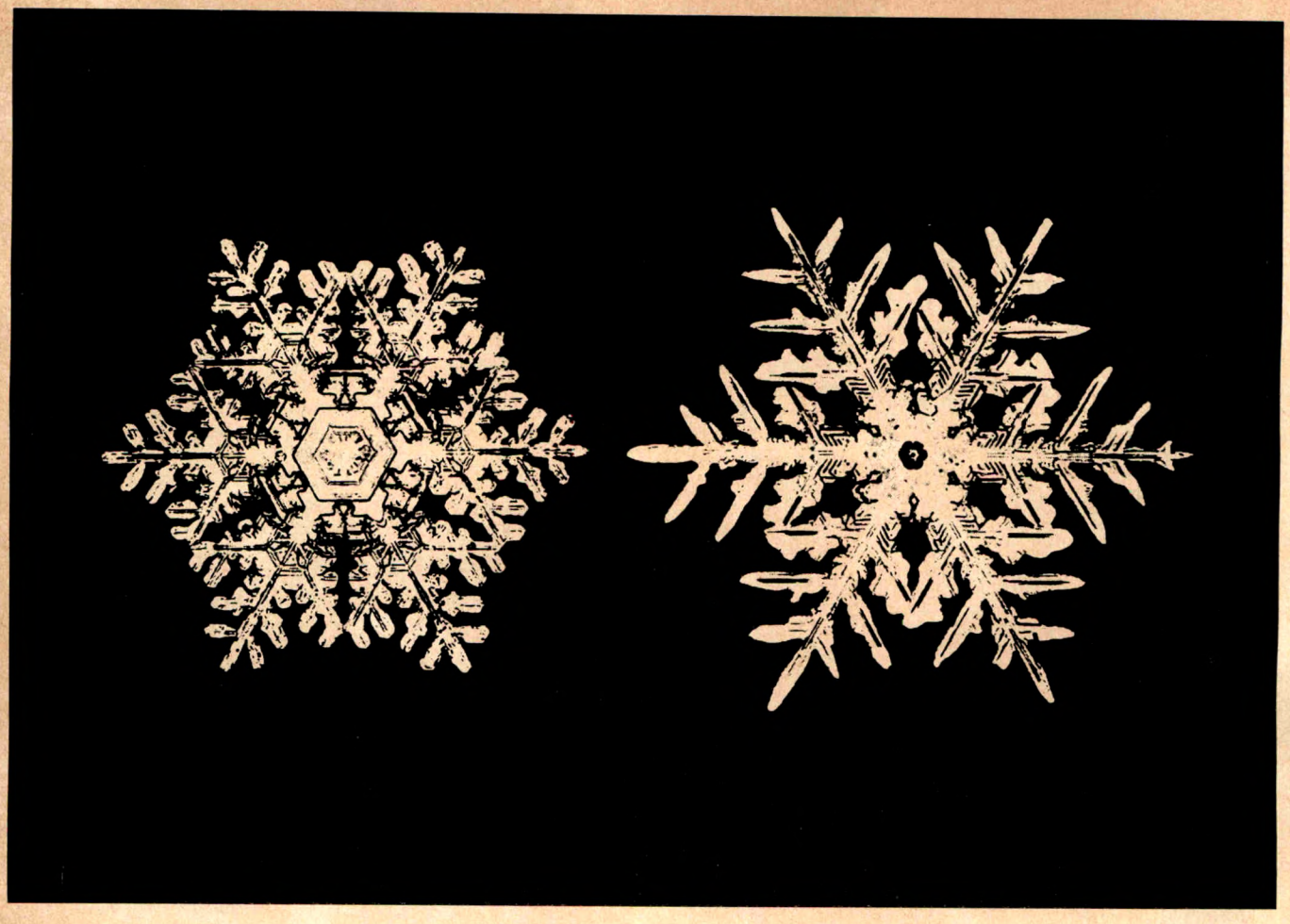
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No two are exactly alike.

Because body chemistry differs from person to person, we often need a choice of drugs to treat the same illness.

You've heard it said that no two snowflakes are exactly alike. The variety is endless. Much the same is true of the human body.

Take the case of two patients suffering from hypertension. Both under the care of the same physician, who prescribes the same medication for each. One patient responds to the medication while the other reports unpleasant side-effects. Thanks to the diversity of drugs available to treat this illness, the doctor is able to prescribe another medicine that works without the side effects.

To maintain the high standards of quality care, and because some drugs work better than others on different people, it is essential to have this diversity.

America's research-based pharmaceutical companies are committed to providing a wide range of drugs of the highest quality to serve the public. Why? Because the public is made up of different people requiring different treatment—even when they suffer from the same illness.

Pharmaceutical Manufacturers Association

IF A NEW MEDICINE CAN HELP, WE'RE WORKING ON IT.

Now for heart rate control during atrial fibrillation and flutter

CARDIZEM® 5 mg/mL Injectable

(diltiazem hydrochloride)

BOLUS INFUSION



GAINS HEART RATE CONTROL QUICKLY...

CIVAH495/A8113

Cardizem Injectable is indicated for temporary control of rapid ventricular rate during atrial fibrillation and flutter; rarely converts to normal sinus rhythm.

Please the see brief summary of prescribing information on an adjacent page.

6493E2

CARDIZEM® Injectable

(diltiazem hydrochloride)

BOLUS INFUSION



Should be used with continuous monitoring of ECG and blood pressure to avoid hypotension or bradycardia. Infusion rate/dose should be regulated accordingly. A defibrillator and emergency equipment should be readily available.

CIVAH495/A8113

For heart rate control during atrial fibrillation and flutter

MAINTAINS HEART RATE CONTROL SAFELY

FAST

- 3-minute onset of action from first bolus injection[1]
- 95% response rate within 2 to 7 minutes of administration[1]
- 1- to 3-hour duration of action with bolus

SAFE

- 4.3% incidence of asymptomatic hypotension[1]*
- 3.2 % incidence of symptomatic hypotension[1]*
- 3.9% incidence of injection site reaction[1]
- 1.7% incidence of flushing[1]*
- Little negative inotropic effect[1]†
- Do not use in Af/Fl patients with WPW or short PR syndrome

  Other contraindications: sick sinus syndrome and second- or third-degree AV block except with a functioning pacemaker; severe hypotension and shock; hypersensitivity; recent IV beta-blockers; ventricular tachycardia.

CONTINUOUS CONTROL

- Heart rate control through infusion for up to 24 hours[1,2]

  Cardizem Injectable is indicated for temporary control of rapid ventricular rate during atrial fibrillation and flutter; rarely converts to normal sinus rhythm.

*Occurs most often during or immediately following bolus injection.
†Caution should be used in patients with congestive heart failure.

CARDIZEM INJECTABLE
Heart rate control that is fast, safe, and continuous

Please see the brief summary of prescribing information on an adjacent page.

6493E2

CARDIZEM® Injectable (diltiazem hydrochloride) BOLUS INFUSION

CONVENIENT DOSAGE

1	2	3
Beginning treatment as	**If response is inadequate, wait 15 minutes**	**Treatment as**
BOLUS: 0.25 mg/kg actual body weight over 2 minutes	**BOLUS:** 0.35 mg/kg actual body weight over 2 minutes	**INFUSION: 10* to 15 mg/hr**
20 mg average patient	**25 mg average patient**	*5 mg/hr may be appropriate starting infusion for some patients.

BRIEF SUMMARY

CARDIZEM® Injectable
(diltiazem hydrochloride)

INDICATIONS AND USAGE

CARDIZEM Injectable (diltiazem hydrochloride) is indicated for the following:

1. **Atrial Fibrillation or Atrial Flutter.** Temporary control of rapid ventricular rate in atrial fibrillation or atrial flutter. It should not be used in patients with atrial fibrillation or atrial flutter associated with an accessory bypass tract such as in Wolff-Parkinson-White (WPW) syndrome or short PR syndrome.
2. **Paroxysmal Supraventricular Tachycardia.** Rapid conversion of paroxysmal supraventricular tachycardias (PSVT) to sinus rhythm. This includes AV nodal reentrant tachycardias and reciprocating tachycardias associated with an extranodal accessory pathway such as the WPW syndrome or short PR syndrome. Unless otherwise contraindicated, appropriate vagal maneuvers should be attempted prior to administration of CARDIZEM Injectable.

The use of CARDIZEM Injectable for control of ventricular response in patients with atrial fibrillation or atrial flutter or conversion to sinus rhythm in patients with PSVT should be undertaken with caution when the patient is compromised hemodynamically or is taking other drugs that decrease any or all of the following: peripheral resistance, myocardial filling, myocardial contractility, or electrical impulse propagation in the myocardium.

For either indication and particularly when employing continuous intravenous infusion, the setting should include continuous monitoring of the ECG and frequent measurement of blood pressure. A defibrillator and emergency equipment should be readily available.

In domestic controlled trials in patients with atrial fibrillation or atrial flutter, bolus administration of CARDIZEM Injectable was effective in reducing heart rate by at least 20% in 95% of patients. CARDIZEM Injectable rarely converts atrial fibrillation or atrial flutter to normal sinus rhythm. Following administration of one or two intravenous bolus doses of CARDIZEM Injectable, response usually occurs within 3 minutes and maximal heart rate reduction generally occurs in 2 to 7 minutes. Heart rate reduction may last from 1 to 3 hours. If hypotension occurs, it is generally short-lived, but may last from 1 to 3 hours.

A 24-hour continuous infusion of CARDIZEM Injectable in the treatment of atrial fibrillation or atrial flutter maintained at least a 20% heart rate reduction during the infusion in 83% of patients. Upon discontinuation of infusion, heart rate reduction may last from 0.5 hours to more than 10 hours (median duration 7 hours). Hypotension, if it occurs, may be similarly persistent.

In the controlled clinical trials, 3.2% of patients required some form of intervention (typically, use of intravenous fluids or the Trendelenburg position) for blood pressure support following CARDIZEM Injectable.

In domestic controlled trials, bolus administration of CARDIZEM Injectable was effective in converting PSVT to normal sinus rhythm in 88% of patients within 3 minutes of the first or second bolus dose.

Symptoms associated with the arrhythmia were improved in conjunction with decreased heart rate or conversion to normal sinus rhythm following administration of CARDIZEM Injectable.

CONTRAINDICATIONS

CARDIZEM Injectable is contraindicated in:

1. Patients with sick sinus syndrome except in the presence of a functioning ventricular pacemaker.
2. Patients with second- or third-degree AV block except in the presence of a functioning ventricular pacemaker.
3. Patients with severe hypotension or cardiogenic shock.
4. Patients who have demonstrated hypersensitivity to the drug.
5. Intravenous diltiazem and intravenous beta-blockers should not be administered together or in close proximity (within a few hours).
6. Patients with atrial fibrillation or atrial flutter associated with an accessory bypass tract such as in WPW syndrome or short PR syndrome.

   As with other agents which slow AV nodal conduction and do not prolong the refractoriness of the accessory pathway (eg, verapamil, digoxin), in rare instances patients in atrial fibrillation or atrial flutter associated with an accessory bypass tract may experience a potentially life-threatening increase in heart rate accompanied by hypotension when treated with CARDIZEM Injectable. As such, the initial use of CARDIZEM Injectable should be, if possible, in a setting where monitoring and resuscitation capabilities, including DC cardioversion/defibrillation, are present (see OVERDOSAGE). Once familiarity of the patient's response is established, use in an office setting may be acceptable.
7. Patients with ventricular tachycardia. Administration of other calcium channel blockers to patients with wide complex tachycardia (QRS ≥ 0.12 seconds) has resulted in hemodynamic deterioration and ventricular fibrillation. It is important that an accurate pretreatment diagnosis distinguish wide complex QRS tachycardia of supraventricular origin from that of ventricular origin prior to administration of CARDIZEM Injectable.

WARNINGS

1. **Cardiac Conduction.** Diltiazem prolongs AV nodal conduction and refractoriness that may rarely result in second- or third-degree AV block in sinus rhythm. Concomitant use of diltiazem with agents known to affect cardiac conduction may result in additive effects (see Drug Interactions). If high-degree AV block occurs in sinus rhythm, intravenous diltiazem should be discontinued and appropriate supportive measures instituted (see OVERDOSAGE).
2. **Congestive Heart Failure.** Although diltiazem has a negative inotropic effect in isolated animal tissue preparations, hemodynamic studies in humans with normal ventricular function and in patients with a compromised myocardium, such as severe CHF, acute MI, and hypertrophic cardiomyopathy, have not shown a reduction in cardiac index nor consistent negative effects on contractility (dp/dt). Administration of oral diltiazem in patients with acute myocardial infarction and pulmonary congestion documented by x-ray on admission is contraindicated. Experience with the use of CARDIZEM Injectable in patients with impaired ventricular function is limited. Caution should be exercised when using the drug in such patients.
3. **Hypotension.** Decreases in blood pressure associated with CARDIZEM Injectable therapy may occasionally result in symptomatic hypotension (3.2%). The use of intravenous diltiazem for control of ventricular response in patients with supraventricular arrhythmias should be undertaken with caution when the patient is compromised hemodynamically. In addition, caution should be used in patients taking other drugs that decrease peripheral resistance, intravascular volume, myocardial contractility or conduction.
4. **Acute Hepatic Injury.** In rare instances, significant elevations in enzymes such as alkaline phosphatase, LDH, SGOT, SGPT, and other phenomena consistent with acute hepatic injury have been noted following oral diltiazem. Therefore, the potential for acute hepatic injury exists following administration of intravenous diltiazem.
5. **Ventricular Premature Beats (VPBs).** VPBs may be present on conversion of PSVT to sinus rhythm with CARDIZEM Injectable. These VPBs are transient, are typically considered to be benign, and appear to have no clinical significance. Similar ventricular complexes have been noted during cardioversion, other pharmacologic therapy, and during spontaneous conversion of PSVT to sinus rhythm.

PRECAUTIONS

General. CARDIZEM (diltiazem hydrochloride) is extensively metabolized by the liver and excreted by the kidneys and in bile. The drug should be used with caution in patients with impaired renal or hepatic function (see WARNINGS). High intravenous dosages (4.5 mg/kg tid) administered to dogs resulted in significant bradycardia and alterations in AV conduction. In subacute and chronic dog and rat studies designed to produce toxicity, high oral doses of diltiazem were associated with hepatic damage. In special subacute hepatic studies, oral doses of 125 mg/kg and higher in rats were associated with histological changes in the liver, which were reversible when the drug was discontinued. In dogs, oral doses of 20 mg/kg were also associated with hepatic changes; however, these changes were reversible with continued dosing.

Dermatologic events progressing to erythema multiforme and/or exfoliative dermatitis have been infrequently reported following oral diltiazem. Therefore, the potential for these dermatologic reactions exists following exposure to intravenous diltiazem. Should a dermatologic reaction persist, the drug should be discontinued.

Drug Interactions. Due to potential for additive effects, caution is warranted in patients receiving CARDIZEM Injectable concomitantly with any agent(s) known to affect cardiac contractility and/or SA or AV node conduction (see WARNINGS).

As with all drugs, care should be exercised when treating patients with multiple medications. CARDIZEM undergoes extensive metabolism by the cytochrome P-450 mixed function oxidase system. Although specific pharmacokinetic drug-drug interaction studies have not been conducted with single intravenous injection or constant rate intravenous infusion, coadministration of CARDIZEM Injectable with other agents which primarily undergo the same route of biotransformation may result in competitive inhibition of metabolism.

Digitalis: Intravenous diltiazem has been administered to patients receiving either intravenous or oral digitalis therapy. The combination of the two drugs was well tolerated without serious adverse effects. However, since both drugs affect AV nodal conduction, patients should be monitored for excessive slowing of the heart rate and/or AV block.

Beta-blockers: Intravenous diltiazem has been administered to patients on chronic oral beta-blocker therapy. The combination of the two drugs was generally well tolerated without serious adverse effects. If intravenous diltiazem is administered to patients receiving chronic oral beta-blocker therapy, the possibility for bradycardia, AV block, and/or depression of contractility should be considered (see CONTRAINDICATIONS). ***Oral*** administration of diltiazem with propranolol in five normal volunteers resulted in increased propranolol levels in all subjects and bioavailability of propranolol was increased approximately 50%. In vitro, propranolol appears to be displaced from its binding sites by diltiazem.

Anesthetics: The depression of cardiac contractility, conductivity, and automaticity as well as the vascular dilation associated with anesthetics may be potentiated by calcium channel blockers. When used concomitantly, anesthetics and calcium blockers should be titrated carefully.

Carcinogenesis, Mutagenesis, Impairment of Fertility. A 24-month study in rats at oral dosage levels of up to 100 mg/kg/day, and a 21-month study in mice at oral dosage levels of up to 30 mg/kg/day showed no evidence of carcinogenicity. There was also no mutagenic response in vitro or in vivo in mammalian cell assays or in vitro in bacteria. No evidence of impaired fertility was observed in a study performed in male and female rats at oral dosages of up to 100 mg/kg/day.

Pregnancy. Category C. Reproduction studies have been conducted in mice, rats, and rabbits. Administration of oral doses ranging from five to ten times greater (on a mg/kg basis) than the daily recommended oral antianginal therapeutic dose has resulted in embryo and fetal lethality. These doses, in some studies, have been reported to cause skeletal abnormalities. In the perinatal/postnatal studies there was some reduction in early individual pup weights and survival rates. There was an increased incidence of stillbirths at doses of 20 times the human oral antianginal dose or greater.

There are no well-controlled studies in pregnant women; therefore, use CARDIZEM in pregnant women only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers. Diltiazem is excreted in human milk. One report with oral diltiazem suggests that concentrations in breast milk may approximate serum levels. If use of CARDIZEM is deemed essential, an alternative method of infant feeding should be instituted.

Pediatric Use. Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

The following adverse reaction rates are based on the use of CARDIZEM Injectable in over 400 domestic clinical trial patients with atrial fibrillation/flutter or PSVT under double-blind or open-label conditions. Worldwide experience in over 1,300 patients was similar.

Adverse events reported in controlled and uncontrolled clinical trials were generally mild and transient. Hypotension was the most commonly reported adverse event during clinical trials. Asymptomatic hypotension occurred in 4.3% of patients. Symptomatic hypotension occurred in 3.2% of patients. When treatment for hypotension was required, it generally consisted of administration of saline or placing the patient in the Trendelenburg position. Other events reported in at least 1% of the diltiazem-treated patients were injection site reactions (eg, itching, burning)—3.9%, vasodilation (flushing)—1.7%, and arrhythmia (junctional rhythm or isorhythmic dissociation)—1.0%.

In addition, the following events were reported infrequently (less than 1%):

Cardiovascular:	Atrial flutter, AV block first degree, AV block second degree, bradycardia, chest pain, congestive heart failure, sinus pause, sinus node dysfunction, syncope, ventricular arrhythmia, ventricular fibrillation, ventricular tachycardia.
Dermatologic:	Pruritus, sweating.
Gastrointestinal:	Constipation, elevated SGOT or alkaline phosphatase, nausea, vomiting.
Nervous System:	Dizziness, paresthesia.
Other:	Amblyopia, asthenia, dry mouth, dyspnea, edema, headache, hyperuricemia.

Although not observed in clinical trials with CARDIZEM Injectable, other reactions associated with oral diltiazem may occur.

Product information as of October 1991

References: 1. Cardizem Injectable prescribing information. 2. Ellenbogen KA, Dias VC, Plumb VJ, Heywood JT, Mirvis DM. *J Am Coll Cardiol.* 1991;18:891-897.

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PRESCRIPTION PRODUCTS DIVISION
KANSAS CITY, MO 64114

CARDIZEM INJECTABLE...HEART RATE CONTROL THAT IS FAST, SAFE, AND CONTINUOUS

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Frequency and Outcome of Chest Pain After Two New Coronary Interventions (Atherectomy and Stenting)

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Between June 1988 and July 1991, 464 new device interventions were performed in 410 patients. Chest pain occurred within 72 hours after the procedure in 94 patients (23%). All 14 patients with abnormal angiography had electrocardiographic changes. Non-Q-wave myocardial infarction occurred in 22 of 395 patients (5%) (29% with chest pain and electrocardiographic changes, 7% with chest pain and no electrocardiographic change, and 3% without chest pain). A decreased percent residual stenosis, incomplete revascularization and the presence of multivessel disease are associated with chest pain after new device intervention. Therefore, patients with chest pain but no electrocardiographic changes early after successful stenting or atherectomy need not undergo urgent recatheterization.

1383

A Patency-Oriented Strategy for Early Management of Acute Myocardial Infarction Using Emergency Coronary Angiography and Selective Coronary Angioplasty

Jean-Michel Juliard, P. Gabriel Steg, Dominique Himbert, Alain Cohen-Solal, Marie-Claude Aumont, and René Gourgon

Infarct-related artery patency is a strong prognostic factor after acute myocardial infarction. One hundred fifty consecutive patients with acute myocardial infarction (<6 hours) were managed according to a strategy designed to provide infarct-related artery patency for the maximum number. Intravenous thrombolysis was the usual treatment (n = 103), followed by emergency coronary angiography (90 minutes after beginning of thrombolysis) in 98 patients, which identified 31 thrombolysis failures (32%) and led to 19 attempts at rescue angioplasty. All patients were scheduled for predischarge angiography 5 to 10 days later. Direct angioplasty was performed in 40 patients because of contraindications to thrombolysis, cardiogenic shock, diagnostic doubt or ideal conditions for direct angioplasty, with a 90% success rate. Conventional medical treatment was used in the 7 remaining patients because of age or contraindications to thrombolysis and angioplasty. This strategy achieved a low in-hospital

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What Is A Single-handed Approach To Blood Pressure Reduction



In Many Patients:

One Agent

Once-A-Day*

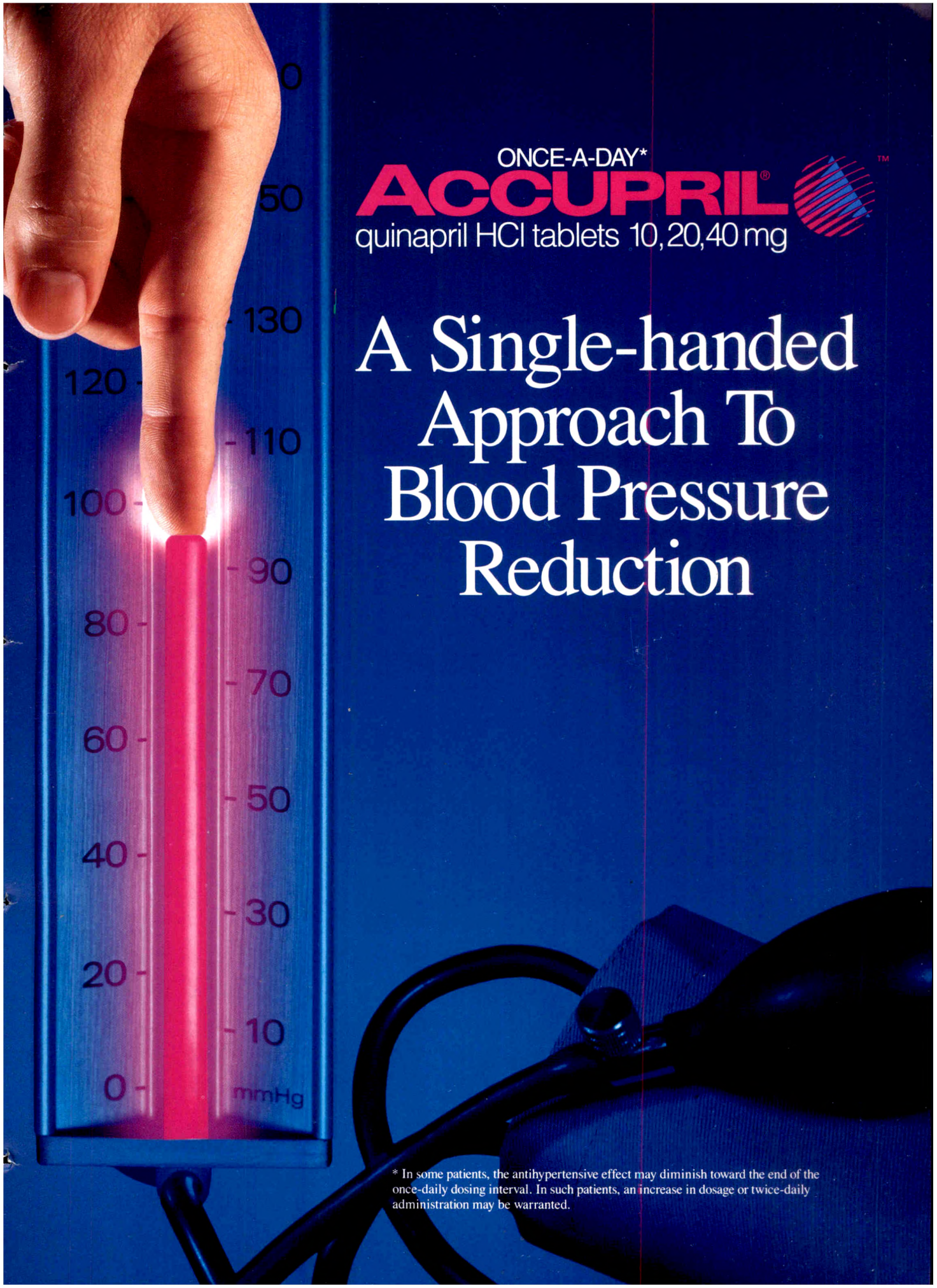
One Price

One price for all tablet
strengths... 10 mg, 20 mg, 40 mg.

* In some patients, the antihypertensive effect may diminish toward the end of the once-daily dosing interval. In such patients, an increase in dosage or twice-daily administration may be warranted.

Accupril is contraindicated in patients who are hypersensitive to this product and in patients with a history of angioedema related to previous treatment with an ACE inhibitor.

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ONCE-A-DAY*
ACCUPRIL®
quinapril HCl tablets 10,20,40 mg
A Single-handed Approach To Blood Pressure Reduction
0
50
130
120
110
100
90
80
70
60
50
40
30
20
10
0
mmHg
* In some patients, the antihypertensive effect may diminish toward the end of the once-daily dosing interval. In such patients, an increase in dosage or twice-daily administration may be warranted.

USE IN PREGNANCY
When used in pregnancy during the second and third trimesters, ACE inhibitors can cause injury and even death to the developing fetus. When pregnancy is detected, ACCUPRIL should be discontinued as soon as possible. See WARNINGS, Fetal/Neonatal Morbidity and Mortality.

Before prescribing, please see full prescribing information. A brief summary follows.

INDICATIONS AND USAGE
ACCUPRIL is indicated for the treatment of hypertension. It may be used alone or in combination with thiazide diuretics.

In using ACCUPRIL, consideration should be given to the fact that another angiotensin-converting enzyme (ACE) inhibitor, captopril, has caused agranulocytosis, particularly in patients with renal impairment or collagen vascular disease. Available data are insufficient to show that ACCUPRIL does not have a similar risk (see WARNINGS).

CONTRAINDICATIONS
ACCUPRIL is contraindicated in patients who are hypersensitive to this product and in patients with a history of angioedema related to previous treatment with an ACE inhibitor.

WARNINGS
Angioedema: Angioedema of the face, extremities, lips, tongue, glottis, and larynx has been reported in patients treated with ACE inhibitors and has been seen in 0.1% of patients receiving ACCUPRIL. Angioedema associated with laryngeal edema can be fatal. If laryngeal stridor or angioedema of the face, tongue, or glottis occurs, treatment with ACCUPRIL should be discontinued immediately, the patient treated in accordance with accepted medical care, and carefully observed until the swelling disappears. In instances where swelling is confined to the face and lips, the condition generally resolves without treatment; antihistamines may be useful in relieving symptoms. **Where there is involvement of the tongue, glottis, or larynx likely to cause airway obstruction, emergency therapy including, but not limited to, subcutaneous epinephrine solution 1:1000 (0.3 to 0.5 mL) should be promptly administered (see ADVERSE REACTIONS).**

Hypotension: Symptomatic hypotension was rarely seen in uncomplicated hypertensive patients treated with ACCUPRIL but, as with other ACE inhibitors, it is a possible consequence of therapy in salt/volume depleted patients, such as those previously treated with diuretics or dietary salt restriction or who are on dialysis (see PRECAUTIONS, DRUG INTERACTIONS, and ADVERSE REACTIONS). In controlled studies, syncope was observed in 0.4% of patients (N = 3203); this incidence was similar to that observed for captopril (1%) and enalapril (0.8%).

In patients with concomitant congestive heart failure, with or without associated renal insufficiency, ACE inhibitor therapy may cause excessive hypotension, which may be associated with oliguria or azotemia and, rarely, with acute renal failure and death. In such patients, ACCUPRIL therapy should be started at the recommended dose under close medical supervision. These patients should be followed closely for the first 2 weeks of treatment and whenever the dosage of antihypertensive medication is increased (see DOSAGE AND ADMINISTRATION).

If symptomatic hypotension occurs, the patient should be placed in the supine position and, if necessary, normal saline may be administered intravenously. A transient hypotensive response is not a contraindication to further doses; however, lower doses of ACCUPRIL or reduced concomitant diuretic therapy should be considered.

Neutropenia/Agranulocytosis: Another ACE inhibitor, captopril, has been shown to cause agranulocytosis and bone marrow depression rarely in patients with uncomplicated hypertension, but more frequently in patients with renal impairment, especially if they also have a collagen vascular disease such as systemic lupus erythematosus or scleroderma. Agranulocytosis did occur during ACCUPRIL treatment in one patient with a history of neutropenia during previous captopril therapy. Available data from clinical trials of ACCUPRIL are insufficient to show that, in patients without prior reactions to other ACE inhibitors, ACCUPRIL does not cause agranulocytosis at similar rates. As with other ACE inhibitors, periodic monitoring of white blood cell counts in patients with collagen vascular disease and/or renal disease should be considered.

Fetal/Neonatal Morbidity and Mortality: ACE inhibitors can cause fetal and neonatal morbidity and death when administered to pregnant women. Several dozen cases have been reported in the world literature. When pregnancy is detected, ACE inhibitors should be discontinued as soon as possible.

The use of ACE inhibitors during the second and third trimesters of pregnancy has been associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death. Oligohydramnios has also been reported, presumably resulting from decreased fetal renal function; oligohydramnios in this setting has been associated with fetal limb contractures, craniofacial deformation, and hypoplastic lung development. Prematurity, intrauterine growth retardation, and patent ductus arteriosus have also been reported, although it is not clear whether these occurrences were due to the ACE inhibitor exposure.

These adverse effects do not appear to have resulted from intrauterine ACE inhibitor exposure that has been limited to the first trimester. Mothers whose embryos and fetuses are exposed to ACE inhibitors only during the first trimester should be so informed. Nonetheless, when patients become pregnant, physicians should make every effort to discontinue the use of ACCUPRIL as soon as possible.

Rarely (probably less often than once in every thousand pregnancies), no alternative to ACE inhibitors will be found. In these rare cases, the mothers should be apprised of the potential hazards to their fetuses, and serial ultrasound examinations should be performed to assess the intraamniotic environment.

If oligohydramnios is observed, ACCUPRIL should be discontinued unless it is considered life-saving for the mother. Contraction stress testing (CST), a non-stress test (NST), or biophysical profiling (BPP) may be appropriate, depending upon the week of pregnancy. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury.

Infants with histories of *in utero* exposure to ACE inhibitors should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion. Exchange transfusion or dialysis may be required as a means of reversing hypotension and/or substituting for disordered renal function. Removal of ACCUPRIL, which crosses the placenta, from the neonatal circulation is not significantly accelerated by these means.

No teratogenic effects of ACCUPRIL were seen in studies of pregnant rats and rabbits. On a mg/kg basis, the doses used were up to 180 times (in rats) and one time (in rabbits) the maximum recommended human dose.

PRECAUTIONS
General
Impaired renal function: As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients with severe heart failure whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with ACE inhibitors, including ACCUPRIL, may be associated with oliguria and/or progressive azotemia and rarely acute renal failure and/or death.

In clinical studies in hypertensive patients with unilateral or bilateral renal artery stenosis, increases in blood urea nitrogen and serum creatinine have been observed in some patients following ACE inhibitor therapy. These increases were almost always reversible upon discontinuation of the ACE inhibitor and/or diuretic therapy. In such patients, renal function should be monitored during the first few weeks of therapy.

Some hypertensive patients with no apparent preexisting renal vascular disease have developed increases in blood urea and serum creatinine, usually minor and transient, especially when ACCUPRIL has been given concomitantly with a diuretic. This is more likely to occur in patients with preexisting renal impairment. Dosage reduction and/or discontinuation of any diuretic and/or ACCUPRIL may be required.

Evaluation of hypertensive patients should always include assessment of renal function (see DOSAGE AND ADMINISTRATION).

Hyperkalemia and potassium-sparing diuretics: In clinical trials, hyperkalemia (serum potassium ≥5.8 mmol/L) occurred in approximately 2% of patients receiving ACCUPRIL. In most cases, elevated serum potassium levels were isolated values which resolved despite continued therapy. Less than 0.1% of patients discontinued therapy due to hyperkalemia. Risk factors for the development of hyperkalemia include renal insufficiency, diabetes mellitus, and the concomitant use of potassium-sparing diuretics, potassium supplements, and/or potassium-containing salt substitutes, which should be used cautiously, if at all, with ACCUPRIL (see PRECAUTIONS, Drug Interactions).

Cough: Cough has been reported with the use of ACE inhibitors. Characteristically, the cough is nonproductive, persistent, and resolves after discontinuation of therapy. ACE inhibitor-induced cough should be considered as part of the differential diagnosis of cough.

Surgery/anesthesia: In patients undergoing major surgery or during anesthesia with agents that produce hypotension, ACCUPRIL will block angiotensin II formation secondary to compensatory renin release. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by volume expansion.

Information for Patients
Pregnancy: Female patients of childbearing age should be told about the consequences of second- and third-trimester exposure to ACE inhibitors, and they should also be told that these consequences do not appear to have resulted from intrauterine ACE-inhibitor exposure that has been limited to the first trimester. These patients should be asked to report pregnancies to their physicians as soon as possible.

Angioedema: Angioedema, including laryngeal edema, can occur with treatment with ACE inhibitors, especially following the first dose. Patients should be so advised and told to report immediately any signs or symptoms suggesting angioedema (swelling of face, extremities, eyes, lips, tongue, difficulty in swallowing or breathing) and to stop taking the drug until they have consulted with their physician (see WARNINGS).

Symptomatic hypotension: Patients should be cautioned that lightheadedness can occur, especially during the first few days of ACCUPRIL therapy, and that it should be reported to a physician. If actual syncope occurs, patients should be told to not take the drug until they have consulted with their physician (see WARNINGS).

All patients should be cautioned that inadequate fluid intake or excessive perspiration, diarrhea, or vomiting can lead to an excessive fall in blood pressure because of reduction in fluid volume, with the same consequences of lightheadedness and possible syncope.

Patients planning to undergo any surgery and/or anesthesia should be told to inform their physician that they are taking an ACE inhibitor.

Hyperkalemia: Patients should be told not to use potassium supplements or salt substitutes containing potassium without consulting their physician (see PRECAUTIONS).

Neutropenia: Patients should be told to report promptly any indication of infection (eg, sore throat, fever) which could be a sign of neutropenia.

NOTE: As with many other drugs, certain advice to patients being treated with ACCUPRIL is warranted. This information is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects.

Drug Interactions
Concomitant diuretic therapy: As with other ACE inhibitors, patients on diuretics, especially those on recently instituted diuretic therapy, may occasionally experience an excessive reduction of blood pressure after initiation of therapy with ACCUPRIL. The possibility of hypotensive effects with ACCUPRIL may be minimized by either discontinuing the diuretic or cautiously increasing salt intake prior to initiation of treatment with ACCUPRIL. If it is not possible to discontinue the diuretic, the starting dose of quinapril should be reduced (see DOSAGE AND ADMINISTRATION).

Agents increasing serum potassium: Quinapril can attenuate potassium loss caused by thiazide diuretics and increase serum potassium when used alone. If concomitant therapy of ACCUPRIL with potassium-sparing diuretics (eg, spironolactone, triamterene, or amiloride), potassium supplements, or potassium-containing salt substitutes is indicated, they should be used with caution along with appropriate monitoring of serum potassium (see PRECAUTIONS).

Tetracycline and other drugs that interact with magnesium: Simultaneous administration of tetracycline with ACCUPRIL reduced the absorption of tetracycline by approximately 28% to 37%, possibly due to the high magnesium content in ACCUPRIL tablets. This interaction should be considered if coprescribing ACCUPRIL and tetracycline or other drugs that interact with magnesium.

Lithium: Increased serum lithium levels and symptoms of lithium toxicity have been reported in patients receiving concomitant lithium and ACE inhibitor therapy. These drugs should be co-administered with caution, and frequent monitoring of serum lithium levels is recommended. If a diuretic is also used, it may increase the risk of lithium toxicity.

Other agents: Drug interaction studies of ACCUPRIL with other agents showed:
- Multiple dose therapy with propranolol or cimetidine has no effect on the pharmacokinetics of single doses of ACCUPRIL.
- The anticoagulant effect of a single dose of warfarin (measured by prothrombin time) was not significantly changed by quinapril coadministration twice-daily.
- ACCUPRIL treatment did not affect the pharmacokinetics of digoxin.
- No pharmacokinetic interaction was observed when single doses of ACCUPRIL and hydrochlorothiazide were administered concomitantly.

Carcinogenesis, Mutagenesis, Impairment of Fertility
Quinapril hydrochloride was not carcinogenic in mice or rats when given in doses up to 75 or 100 mg/kg/day (50 to 60 times the maximum human daily dose, respectively, on a mg/kg basis and 3.8 to 10 times the maximum human daily dose when based on a mg/m^2 basis) for 104 weeks. Female rats given the highest dose level had an increased incidence of mesenteric lymph node hemangiomas and skin/subcutaneous lipomas. Neither quinapril nor quinaprilat were mutagenic in the Ames bacterial assay with or without metabolic activation. Quinapril was also negative in the following genetic toxicology studies: *in vitro* mammalian cell point mutation, sister chromatid exchange in cultured mammalian cells, micronucleus test with mice, *in vitro chromosome* aberration with V79 cultured lung cells, and in an *in vivo* cytogenetic study with rat bone marrow. There were no adverse effects on fertility or reproduction in rats at doses up to 100 mg/kg/day (60 and 10 times the maximum daily human dose when based on mg/kg and mg/m^2, respectively).

Pregnancy
Pregnancy Categories C (first trimester) and D (second and third trimesters): See WARNINGS, Fetal/Neonatal Morbidity and Mortality

Nursing Mothers
It is not known if quinapril or its metabolites are secreted in human milk. Quinapril is secreted to a limited extent, however, in milk of lactating rats (5% or less of the plasma drug concentration was found in rat milk). Because many drugs are secreted in human milk, caution should be exercised when ACCUPRIL is given to a nursing mother.

Geriatric Use
Elderly patients exhibited increased area under the plasma concentration time curve (AUC) and peak levels for quinaprilat compared to values observed in younger patients; this appeared to relate to decreased renal function rather than to age itself. In controlled and uncontrolled studies of ACCUPRIL where 918 (21%) patients were 65 years and older, no overall differences in effectiveness or safety were observed between older and younger patients. However, greater sensitivity of some older individual patients cannot be ruled out.

Pediatric Use
The safety and effectiveness of ACCUPRIL in children have not been established.

ADVERSE REACTIONS
ACCUPRIL has been evaluated for safety in 4960 subjects and patients. Of these, 3203 patients, including 655 elderly patients, participated in controlled clinical trials. ACCUPRIL has been evaluated for long-term safety in over 1400 patients treated for 1 year or more.

Adverse experiences were usually mild and transient.

Discontinuation of therapy because of adverse events was required in 4.7% of patients treated with ACCUPRIL in placebo-controlled hypertension trials.

Adverse experiences probably or possibly related to therapy or of unknown relationship to therapy occurring in 1% or more of the 1563 patients in placebo-controlled hypertension trials who were treated with ACCUPRIL are shown below.

Adverse Events in Placebo-Controlled Trials

	ACCUPRIL (N = 1563) Incidence (Discontinuance)	Placebo (N = 579) Incidence (Discontinuance)
Headache	5.6 (0.7)	10.9 (0.7)
Dizziness	3.9 (0.8)	2.6 (0.2)
Fatigue	2.6 (0.3)	1.0
Coughing	2.0 (0.5)	0.0
Nausea/Vomiting	1.4 (0.3)	1.9 (0.2)
Abdominal Pain	1.0 (0.2)	0.7

See PRECAUTIONS, Cough.

Clinical adverse experiences probably or possibly related, or of uncertain relationship to therapy, occurring in 0.5% to 1.0% (except as noted) of the patients treated with ACCUPRIL (with or without concomitant diuretic) in controlled or uncontrolled trials (N = 4397) and less frequent, clinically significant events seen in clinical trials or post-marketing experience (the rarer events are in italics) include (listed by body system):

General: back pain, malaise

Cardiovascular: palpitation, vasodilation, tachycardia, *heart failure, hyperkalemia, myocardial infarction, cerebrovascular accident, hypertensive crisis, angina pectoris, orthostatic hypotension, cardiac rhythm disturbances*

Gastrointestinal: dry mouth or throat, constipation, *gastrointestinal hemorrhage, pancreatitis, abnormal liver function tests*

Nervous/Psychiatric: somnolence, vertigo, syncope, *nervousness, depression*

Integumentary: increased sweating, pruritus, *exfoliative dermatitis, photosensitivity reaction*

Urogenital: *acute renal failure*

Other: amblyopia, pharyngitis, sinusitis, bronchitis, *agranulocytosis, thrombocytopenia*

Fetal/Neonatal Morbidity and Mortality
See WARNINGS, Fetal/Neonatal Morbidity and Mortality.

Angioedema: angioedema has been reported in patients receiving ACCUPRIL (0.1%). Angioedema associated with laryngeal edema may be fatal. If angioedema of the face, extremities, lips, tongue, glottis, and/or larynx occurs, treatment with ACCUPRIL should be discontinued and appropriate therapy instituted immediately. (See WARNINGS.)

Clinical Laboratory Test Findings
Hematology: (See WARNINGS)
Hyperkalemia: (See PRECAUTIONS)
Creatinine and blood urea nitrogen: Increases (↑1.25 times the upper limit of normal) in serum creatinine and blood urea nitrogen were observed in 2% and 2%, respectively, of patients treated with ACCUPRIL alone. Increases are more likely to occur in patients receiving concomitant diuretic therapy than in those on ACCUPRIL alone. These increases often remit on continued therapy.

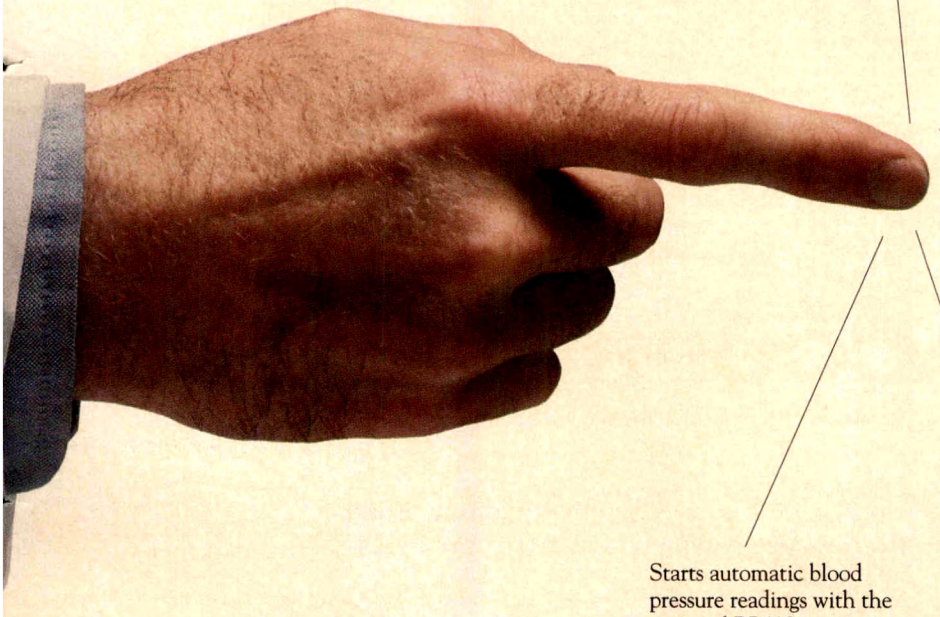
*In some patients, the antihypertensive effect may diminish toward the end of the once-daily dosing interval. In such patients, an increase in dosage or twice-daily administration may be warranted.

ONCE-A-DAY*
ACCUPRIL®
quinapril HCl tablets

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mortality rate (7 of 150 patients [4.7%]; 1.9% in those treated with thrombolysis) and a high infarct-related artery patency rate (both in acute phase [88%] and at hospital discharge [93% of those with a predischarge angiogram; >81% of survivors]), whereas only 3.3% of patients had no benefit from early recanalization therapy. A high proportion of patients (39%) needed emergency angioplasty during the acute phase.

1389

Safety of Combined Intravenous Beta-Adrenergic Blockade (Atenolol or Metoprolol) and Thrombolytic Therapy in Acute Myocardial Infarction

Belinda K. W. Green, Gary D. Gordon, Adrian R. Horak, Robert N. Scott Millar, and Patrick J. Commerford

One hundred thirty-one patients presenting within 6 hours of onset of symptoms of acute myocardial infarction were treated with intravenous thrombolytic therapy, oral aspirin and heparin. One hundred eleven (85%) were also given intravenous β blockers followed by long-term oral therapy. Twenty-one (19%) discontinued the β blocker because of complications, and 5 (4.5%) required the addition of treatment for heart failure. During follow-up, 6 patients (5%) discontinued therapy after complete mechanical revascularization. Long-term treatment continued in 90 patients (69%) over a 2-year follow-up period. It is concluded that intravenous β-adrenergic blockade is well tolerated in most patients presenting with acute myocardial infarction treated with thrombolytic drugs.

1393

Effectiveness and Safety of a Single Intravenous Bolus Injection of Tissue-Type Plasminogen Activator in Acute Myocardial Infarction

David Hackett, Felicita Andreotti, Agha W. Haider, Claudio Brunelli, Manjit Shahi, Anne Fussell, Nigel Buller, Rodney Foale, David Lipkin, Salvatore Caponnetto, Graham Davies, and Attilio Maseri, and the Bolus Dose-Escalation Study of Tissue-Type Plasminogen Activator (BEST) Investigators

In this Bolus Dose-Escalation Study of Tissue-Type Plasminogen Activator (BEST), the efficacy of 3 different doses of a single rapid intravenous bolus injection of tissue-type plasminogen activator (t-PA) (duteplase, Wellcome Foundation, London) in inducing coronary patency in 64 patients with acute myocardial infarction <6 hours after onset of symptoms was investigated. At 60 minutes after administration of t-PA, the infarct-related coronary artery was patent in 9 of 17 patients (53%) after 0.3 MU/kg, in 14 of 23 (61%) after 0.45 MU/kg and in 10 of 14 (71%) after 0.6 MU/kg. At 90 minutes, coronary patency was present in 9 of 17 cases (53%) after 0.3 MU/kg, in 12 of 24 (50%) after 0.45 MU/kg and in 10 of 13 (77%) after 0.6 MU/kg. One patient in each dose group had a silent reoccluded infarct-related artery by 24 hours, and there were no major bleeding events. A single intravenous bolus injection of 0.6 MU/kg of t-PA appears to be effective in inducing rapid coronary patency and to be safe in patients with acute myocardial infarction.

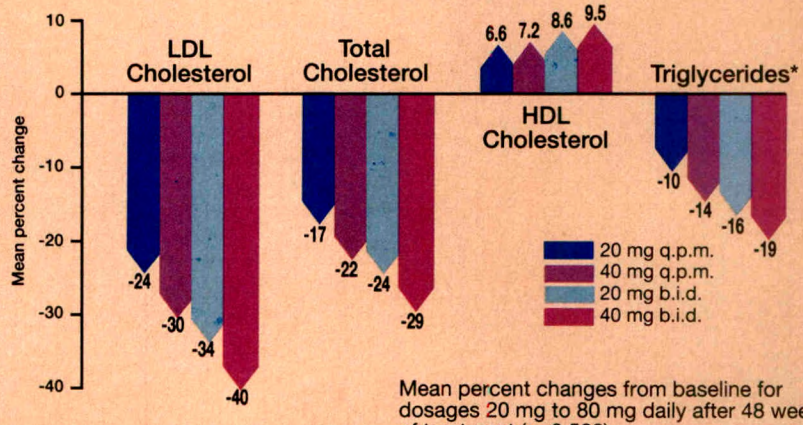
Continued on page A25

The largest U.S. double-blind, placebo-controlled trial of patients with moderate hypercholesterolemia

8,245 patients | 362 clinical sites | 48 weeks

THE EXCEL STUDY
EXPANDED CLINICAL EVALUATION OF LOVASTATIN

Excellent efficacy in lowering LDL and total cholesterol[1]



Mean percent changes from baseline for dosages 20 mg to 80 mg daily after 48 weeks of treatment (n=6,582)

* Triglyceride values are expressed as median changes.

1. Bradford, R.H. et al.: Expanded clinical evaluation of lovastatin (EXCEL) study results: I. Efficacy in modifying plasma lipoproteins and adverse event profile in 8,245 patients with moderate hypercholesterolemia, Arch. Intern. Med. *151*:43-49, January 1991.

For many patients with primary hypercholesterolemia (Types IIa and IIb) when diet and other nondrug therapies are inadequate

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(LOVASTATIN)

Tablets: 10 mg, 20 mg, 40 mg

Proven in research. Proven in practice.

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MEVACOR is contraindicated in patients who are hypersensitive to any component of the medication; in patients with active liver disease or unexplained persistent transaminase elevations; in pregnant or lactating patients; and in women of childbearing age, except when such patients are highly unlikely to conceive.

For complete details on MEVACOR, including cautionary information regarding myopathy, drug interactions, and liver enzyme monitoring, please refer to the Prescribing Information.

For a brief summary of Prescribing Information, please see the next page of this advertisement.

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MEVACOR® *
(LOVASTATIN)

CONTRAINDICATIONS: Hypersensitivity to any component of this medication.

Active liver disease or unexplained persistent elevations of serum transaminases (see WARNINGS).

Pregnancy and lactation.

Atherosclerosis is a chronic process, and the discontinuation of lipid-lowering drugs during pregnancy should have little impact on the outcome of long-term therapy of primary hypercholesterolemia. Moreover, cholesterol and other products of the cholesterol biosynthesis pathway are essential components for fetal development, including synthesis of steroids and cell membranes. Because of the ability of inhibitors of HMG-CoA reductase such as MEVACOR to decrease the synthesis of cholesterol and possibly other products of the cholesterol biosynthesis pathway, MEVACOR may cause fetal harm when administered to a pregnant woman. Therefore, lovastatin is contraindicated during pregnancy. Lovastatin should be administered to women of childbearing age only when such patients are highly unlikely to conceive. If the patient becomes pregnant while taking this drug, lovastatin should be discontinued, and the patient should be apprised of the potential hazard to the fetus.

WARNINGS: *Liver Dysfunction:* Marked persistent increases (to more than 3 times the upper limit of normal) in serum transaminases occurred in 1.9% of adult patients who received lovastatin for at least 1 year in early clinical trials (see ADVERSE REACTIONS). When the drug was interrupted or discontinued in these patients, the transaminase levels usually fell slowly to pretreatment levels. The increases usually appeared 3 to 12 months after the start of therapy with lovastatin and were not associated with jaundice or other clinical signs or symptoms. There was no evidence of hypersensitivity. In the EXCEL study (see CLINICAL PHARMACOLOGY, *Clinical Studies* in the full Prescribing Information), the incidence of marked persistent increases in serum transaminases over 48 weeks was 0.1% for placebo, 0.1% at 20 mg/day, 0.9% at 40 mg/day, and 1.5% at 80 mg/day in patients on lovastatin. However, in post-marketing experience with MEVACOR, symptomatic liver disease has been reported rarely at all dosages (see ADVERSE REACTIONS).

It is recommended that liver function tests be performed during therapy with lovastatin. Serum transaminases, including ALT (SGPT), should be monitored before treatment begins, every 6 weeks during the first 3 months, every 8 weeks during the remainder of the first year, and periodically thereafter (e.g., at approximately 6-month intervals). Special attention should be paid to patients who develop elevated serum transaminase levels, and, in these patients, measurements should be repeated promptly and then performed more frequently. If the transaminase levels show evidence of progression, particularly if they rise to 3 times the upper limit of normal and are persistent, the drug should be discontinued. Liver biopsy should be considered if elevations are persistent beyond the discontinuation of the drug.

The drug should be used with caution in patients who consume substantial quantities of alcohol and/or have a past history of liver disease. Active liver disease or unexplained transaminase elevations are contraindications to the use of lovastatin.

As with other lipid-lowering agents, moderate (less than 3 times the upper limit of normal) elevations of serum transaminases have been reported following therapy with MEVACOR (see ADVERSE REACTIONS). These changes appeared soon after initiation of therapy with MEVACOR, were often transient, were not accompanied by any symptoms, and interruption of treatment was not required.

Skeletal Muscle: **Rhabdomyolysis has been associated with lovastatin therapy alone, when combined with immunosuppressive therapy including cyclosporine in cardiac transplant patients, and when combined in non-transplant patients with either gemfibrozil or lipid-lowering doses (≥1g/day) of nicotinic acid. Some of the affected patients had preexisting renal insufficiency, usually as a consequence of long-standing diabetes. Acute renal failure from rhabdomyolysis has been seen more commonly with the lovastatin-gemfibrozil combination and has also been reported in transplant patients receiving lovastatin plus cyclosporine.**

Rhabdomyolysis with or without renal impairment has been reported in seriously ill patients receiving erythromycin concomitantly with lovastatin. Therefore, patients receiving concomitant lovastatin and erythromycin should be carefully monitored.

Fulminant rhabdomyolysis has been seen as early as 3 weeks after initiation of combined therapy with gemfibrozil and lovastatin, but may be seen after several months. For these reasons, it is felt that, in most subjects who have had an unsatisfactory lipid response to either drug alone, the possible benefits of combined therapy with lovastatin and gemfibrozil do not outweigh the risks of severe myopathy, rhabdomyolysis, and acute renal failure. While it is not known whether this interaction occurs with fibrates other than gemfibrozil, myopathy and rhabdomyolysis have occasionally been associated with the use of other fibrates alone, including clofibrate. Therefore, the combined use of lovastatin with other fibrates should generally be avoided.

Physicians contemplating combined therapy with lovastatin and lipid-lowering doses of nicotinic acid or with immunosuppressive drugs should carefully weigh the potential benefits and risks and should carefully monitor patients for any signs and symptoms of muscle pain, tenderness, or weakness, particularly during the initial months of therapy and during any periods of upward dosage titration of either drug. Periodic creatine phosphokinase (CPK) determinations may be considered in such situations, but there is no assurance that such monitoring will prevent the occurrence of severe myopathy. The monitoring of lovastatin drug and metabolite levels may be considered in transplant patients who are treated with immunosuppressives and lovastatin.

Lovastatin therapy should be temporarily withheld or discontinued in any patient with an acute, serious condition suggestive of a myopathy or having a risk factor predisposing to the development of renal failure secondary to rhabdomyolysis, including: severe acute infection, hypotension, major surgery, trauma, severe metabolic, endocrine, and electrolyte disorders, and uncontrolled seizures.

Myalgia has been associated with lovastatin therapy. Transient, mildly elevated CPK levels are commonly seen in lovastatin-treated patients. However, in early clinical trials, approximately 0.5% of patients developed a myopathy, i.e., myalgia or muscle weakness associated with markedly elevated CPK levels. In the EXCEL study (see CLINICAL PHARMACOLOGY, *Clinical Studies* in the full Prescribing Information), 5 patients (0.1%) taking lovastatin alone (1 at 40 mg q.p.m. and 4 at 40 mg b.i.d.) developed myopathy (muscle symptoms and CPK levels >10 times the upper limit of normal). Myopathy should be considered in any patient with diffuse myalgias, muscle tenderness or weakness, and/or marked elevation of CPK. Patients should be advised to report promptly any unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever. Lovastatin therapy should be discontinued if markedly elevated CPK levels occur or myopathy is diagnosed or suspected.

Most of the patients who have developed myopathy (including rhabdomyolysis) while taking lovastatin were receiving concomitant therapy with immunosuppressive drugs, gemfibrozil, or lipid-lowering doses of nicotinic acid. In clinical trials, about 30% of patients on concomitant immunosuppressive therapy including cyclosporine developed myopathy; the corresponding percentages for gemfibrozil and niacin were approximately 5% and 2%, respectively.

In 6 patients with cardiac transplants taking immunosuppressive therapy including cyclosporine concomitantly with lovastatin 20 mg/day, the average plasma level of active metabolites derived from lovastatin was elevated to approximately 4 times the expected levels. Because of an apparent relationship between increased plasma levels of active metabolites derived from lovastatin and myopathy, the daily dosage in patients taking immunosuppressants should not exceed 20 mg/day (see DOSAGE AND ADMINISTRATION). Even at this dosage, the benefits and risks of using lovastatin in patients taking immunosuppressants should be carefully considered.

PRECAUTIONS: *General:* Before instituting therapy with MEVACOR, an attempt should be made to control hypercholesterolemia with appropriate diet, exercise, and weight reduction in obese patients, and to treat other underlying medical problems (see INDICATIONS AND USAGE in the full Prescribing Information).

Lovastatin may elevate CPK and transaminase levels (see WARNINGS and ADVERSE REACTIONS). This should be considered in the differential diagnosis of chest pain in a patient on therapy with lovastatin.

Homozygous Familial Hypercholesterolemia: MEVACOR is less effective in patients with the rare homozygous familial hypercholesterolemia, possibly because these patients have no functional LDL receptors. MEVACOR appears to be more likely to raise serum transaminases (see ADVERSE REACTIONS) in these homozygous patients.

Information for Patients: Patients should be advised to report promptly any unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever.

Drug Interactions: Immunosuppressive Drugs, Gemfibrozil, Niacin (Nicotinic Acid), Erythromycin: See WARNINGS, *Skeletal Muscle.*

Coumarin Anticoagulants: In a small clinical trial in which lovastatin was administered to warfarin-treated patients, no effect on prothrombin time was detected. However, another HMG-CoA reductase inhibitor has been found to produce a less than 2-second increase in prothrombin time in healthy volunteers receiving low doses of warfarin. Also, bleeding and/or increased prothrombin time have been reported in a few patients taking coumarin anticoagulants concomitantly with lovastatin. It is recommended that in patients taking anticoagulants, prothrombin time be determined before starting lovastatin and frequently enough during early therapy to ensure that no significant alteration of prothrombin time occurs. Once a stable prothrombin time has been documented, prothrombin times can be monitored at the intervals usually recommended for patients on coumarin anticoagulants. If the dose of lovastatin is changed, the same procedure should be repeated. Lovastatin therapy has not been associated with bleeding or with changes in prothrombin time in patients not taking anticoagulants.

Antipyrine: Because lovastatin had no effect on the pharmacokinetics of antipyrine or its metabolites, interactions of other drugs metabolized via the same cytochrome isozymes are not expected.

Propranolol: In normal volunteers, there was no clinically significant pharmacokinetic or pharmacodynamic interaction with concomitant administration of single doses of lovastatin and propranolol.

Digoxin: In patients with hypercholesterolemia, concomitant administration of lovastatin and digoxin resulted in no effect on digoxin plasma concentrations.

Other Concomitant Therapy: Although specific interaction studies were not performed, in clinical studies lovastatin was used concomitantly with beta blockers, calcium channel blockers, diuretics, and nonsteroidal anti-inflammatory drugs (NSAIDs) without evidence of clinically significant adverse interactions.

Endocrine Function: HMG-CoA reductase inhibitors interfere with cholesterol synthesis and as such might theoretically blunt adrenal and/or gonadal steroid production. Results of clinical trials with drugs in this class have been inconsistent with regard to drug effects on basal and reserve steroid levels. However, clinical studies have shown that lovastatin does not reduce basal plasma cortisol concentration or impair adrenal reserve and does not reduce basal plasma testosterone concentration. Another HMG-CoA reductase inhibitor has been shown to reduce the plasma testosterone response to HCG. In the same study, the mean testosterone response to HCG was slightly but not significantly reduced after treatment with lovastatin 40 mg daily for 16 weeks in 21 men. The effects of HMG-CoA reductase inhibitors on male fertility have not been studied in adequate numbers of male patients. The effects, if any, on the pituitary-gonadal axis in premenopausal women are unknown. Patients treated with lovastatin who develop clinical evidence of endocrine dysfunction should be evaluated appropriately. Caution should also be exercised if an HMG-CoA reductase inhibitor or other agent used to lower cholesterol levels is administered to patients also receiving other drugs (e.g., ketoconazole, spironolactone, cimetidine) that may decrease the levels or activity of endogenous steroid hormones.

CNS Toxicity: Lovastatin produced optic nerve degeneration (Wallerian degeneration of retinogeniculate fibers) in clinically normal dogs in a dose-dependent fashion starting at 60 mg/kg/day, a dose that produced mean plasma drug levels about 30 times higher than the mean drug level in humans taking the highest recommended dose (as measured by total enzyme inhibitory activity). Vestibulocochlear Wallerian-like degeneration and retinal ganglion cell chromatolysis were also seen in dogs treated for 14 weeks at 180 mg/kg/day, a dose that resulted in a mean plasma drug level (C_{max}) similar to that seen with the 60 mg/kg/day dose.

CNS vascular lesions, characterized by perivascular hemorrhage and edema, mononuclear cell infiltration of perivascular spaces, perivascular fibrin deposits, and necrosis of small vessels, were seen in dogs treated with lovastatin at a dose of 180 mg/kg/day, a dose that produced plasma drug levels (C_{max}) about 30 times higher than the mean values in humans taking 80 mg/day.

Similar optic nerve and CNS vascular lesions have been observed with other drugs of this class.

Carcinogenesis, Mutagenesis, Impairment of Fertility: In a 21-month carcinogenic study in mice, there was a statistically significant increase in the incidence of hepatocellular carcinomas and adenomas in both males and females at 500 mg/kg/day. This dose produced a total plasma drug exposure 3 to 4 times that of humans given the highest recommended dose of lovastatin (drug exposure was measured as total HMG-CoA reductase inhibitory activity in extracted plasma). Tumor increases were not seen at 20 and 100 mg/kg/day, doses that produced drug exposures of 0.3 to 2 times that of humans at the 80 mg/day dose. A statistically significant increase in pulmonary adenomas was seen in female mice at approximately 4 times the human drug exposure. (Although mice were given 300 times the human dose [HD] on an mg/kg body weight basis, plasma levels of total inhibitory activity were only 4 times higher in mice than in humans given 80 mg of MEVACOR® [Lovastatin].)

There was an increase in incidence of papilloma in the nonglandular mucosa of the stomach of mice beginning at exposures of 1 to 2 times that of humans. The glandular mucosa was not affected. The human stomach contains only glandular mucosa.

In a 24-month carcinogenicity study in rats, there was a positive dose-response relationship for hepatocellular carcinogenicity in males at drug exposures 2 to 7 times that of human exposure at 80 mg/day (doses in rats were 5, 30, and 180 mg/kg/day).

A chemically similar drug in this class was administered to mice for 72 weeks at 25, 100, and 400 mg/kg body weight, which resulted in mean serum drug levels approximately 3, 15, and 33 times higher than the mean human serum drug concentration (as total inhibitory activity) after a 40-mg oral dose. Liver carcinomas were significantly increased in high-dose females and mid- and high-dose males, with a maximum incidence of 90% in males. The incidence of adenomas of the liver was significantly increased in mid- and high-dose females. Drug treatment also significantly increased the incidence of lung adenomas in mid- and high-dose males and females. Adenomas of the Harderian gland (a gland of the eye of rodents) were significantly higher in high-dose mice than in controls.

No evidence of mutagenicity was observed in a microbial mutagen test using mutant strains of *Salmonella typhimurium* with or without rat or mouse liver metabolic activation. In addition, no evidence of damage to genetic material was noted in an *in vitro* alkaline elution assay using rat or mouse hepatocytes, a V-79 mammalian cell forward mutation study, an *in vitro* chromosome aberration study in CHO cells, or an *in vivo* chromosomal aberration assay in mouse bone marrow.

Drug-related testicular atrophy, decreased spermatogenesis, spermatocytic degeneration, and giant cell formation were seen in dogs starting at 20 mg/kg/day. Similar findings were seen with another drug in this class. No drug-related effects on fertility were found in studies with lovastatin in rats. However, in studies with a similar drug in this class, there was decreased fertility in male rats treated for 34 weeks at 25 mg/kg body weight, although this effect was not observed in a subsequent fertility study when this same dose was administered for 11 weeks (the entire cycle of spermatogenesis, including epididymal maturation). In rats treated with this same reductase inhibitor at 180 mg/kg/day, seminiferous tubule degeneration (necrosis and loss of spermatogenic epithelium) was observed. No microscopic changes were observed in the testes from rats of either study. The clinical significance of these findings is unclear.

Pregnancy: Pregnancy Category X: See CONTRAINDICATIONS.

Safety in pregnant women has not been established. Lovastatin has been shown to produce skeletal malformations at plasma levels 40 times the human exposure (for mouse fetus) and 80 times the human exposure (for rat fetus) based on mg/m² surface area (doses were 800 mg/kg/day). No drug-induced changes were seen in either species at multiples of 8 times (rat) or 4 times (mouse) the human exposure based on surface area. No evidence of malformations was noted in rabbits at exposures up to 3 times the human exposure (dose of 15 mg/kg/day, highest tolerated dose). MEVACOR should be administered to women of childbearing potential only when such patients are highly unlikely to conceive and have been informed of the potential hazards. If the woman becomes pregnant while taking MEVACOR, it should be discontinued, and the patient advised again as to the potential hazards to the fetus.

Nursing Mothers: It is not known whether lovastatin is excreted in human milk. Because a small amount of another drug in this class is excreted in human breast milk and because of the potential for serious adverse reactions in nursing infants, women taking MEVACOR should not nurse their infants (see CONTRAINDICATIONS).

Pediatric Use: Safety and effectiveness in children and adolescents have not been established. Because children and adolescents are not likely to benefit from cholesterol lowering for at least a decade and because experience with this drug is limited (no studies in subjects below the age of 20 years), treatment of children with lovastatin is not recommended at this time.

ADVERSE REACTIONS: MEVACOR® (Lovastatin) is generally well tolerated; adverse reactions usually have been mild and transient. Less than 1% of patients were discontinued from controlled clinical studies of up to 14 weeks due to adverse experiences attributable to MEVACOR. About 3% of patients were discontinued from extensions of these studies due to adverse experiences attributable to MEVACOR; about half of these patients were discontinued due to increases in serum transaminases. The median duration of therapy in these extensions was 5.2 years.

In the EXCEL study (see CLINICAL PHARMACOLOGY, *Clinical Studies* in the full Prescribing Information), 4.6% of the patients treated up to 48 weeks were discontinued due to clinical or laboratory adverse experiences that were rated by the investigator as possibly, probably, or definitely related to therapy with MEVACOR. The value for the placebo group was 2.5%.

Clinical Adverse Experiences: Adverse experiences reported in patients (%) treated with MEVACOR (n=613) in controlled clinical studies are: *Gastrointestinal:* constipation, 4.9; diarrhea, 5.5; dyspepsia, 3.9; flatus, 6.4; abdominal pain/cramps, 5.7; heartburn, 1.6; nausea, 4.7; *Musculoskeletal:* muscle cramps, 1.1; myalgia, 2.4; *Nervous System/Psychiatric:* dizziness, 2.0; headache, 9.3; *Skin:* rash/pruritus, 5.2; *Special Senses:* blurred vision, 1.5; dysgeusia, 0.8.

Laboratory Tests: Marked persistent increases of serum transaminases have been noted (see WARNINGS).

About 11% of patients had elevations of creatine phosphokinase (CPK) levels of at least twice the normal value on one or more occasions. The corresponding values for the control agents were cholestyramine, 9%, and probucol, 2%. This was attributable to the noncardiac fraction of CPK. Large increases in CPK have sometimes been reported (see WARNINGS, *Skeletal Muscle*).

Expanded Clinical Evaluation of Lovastatin (EXCEL) Study: Clinical Adverse Experiences: MEVACOR was compared to placebo in 8,245 patients with hypercholesterolemia (total cholesterol 240 to 300 mg/dL [6.2–7.8 mmol/L]) in the randomized, double-blind, parallel, 48-week EXCEL study. Clinical adverse experiences reported as possibly, probably, or definitely drug related in ≥1% of any treatment group are shown in the table below. For no event was the incidence on drug and placebo statistically different.

		MEVACOR			
	Placebo (n=1,663) %	20 mg q.p.m. (n=1,642) %	40 mg q.p.m. (n=1,645) %	20 mg b.i.d. (n=1,646) %	40 mg b.i.d. (n=1,649) %
Body as a Whole					
Asthenia	1.4	1.7	1.4	1.5	1.2
Gastrointestinal					
Abdominal pain	1.6	2.0	2.0	2.2	2.5
Constipation	1.9	2.0	3.2	3.2	3.5
Diarrhea	2.3	2.6	2.4	2.2	2.6
Dyspepsia	1.9	1.3	1.3	1.0	1.6
Flatulence	4.2	3.7	4.3	3.9	4.5
Nausea	2.5	1.9	2.5	2.2	2.2
Musculoskeletal					
Muscle cramps	0.5	0.6	0.8	1.1	1.0
Myalgia	1.7	2.6	1.8	2.2	3.0
Nervous System/ Psychiatric					
Dizziness	0.7	0.7	1.2	0.5	0.5
Headache	2.7	2.6	2.8	2.1	3.2
Skin					
Rash	0.7	0.8	1.0	1.2	1.3
Special Senses					
Blurred vision	0.8	1.1	0.9	0.9	1.2

Other clinical adverse experiences reported as possibly, probably, or definitely drug related in 0.5 to 1% of patients in any drug-treated group are listed below. In all these cases, the incidence on drug and placebo was not statistically different. *Body as a Whole:* chest pain; *Gastrointestinal:* acid regurgitation, dry mouth, vomiting; *Musculoskeletal:* leg pain, shoulder pain, arthralgia; *Nervous System/Psychiatric:* insomnia, paresthesia; *Skin:* alopecia, pruritus; *Special Senses:* eye irritation.

Concomitant Therapy: In controlled clinical studies in which lovastatin was administered concomitantly with cholestyramine, no adverse reactions peculiar to this concomitant treatment were observed. The adverse reactions that occurred were limited to those reported previously with lovastatin or cholestyramine. Other lipid-lowering agents were not administered concomitantly with lovastatin during controlled clinical studies. Preliminary data suggest that the addition of either probucol or gemfibrozil to therapy with lovastatin is not associated with greater reduction in LDL cholesterol than that achieved with lovastatin alone. In uncontrolled clinical studies, most of the patients who have developed myopathy were receiving concomitant therapy with immunosuppressive drugs, gemfibrozil, or niacin (nicotinic acid) (see WARNINGS, *Skeletal Muscle*).

The following effects have been reported with drugs in this class:

Skeletal: myopathy, rhabdomyolysis, arthralgias.

Neurological: dysfunction of certain cranial nerves (including alteration of taste, impairment of extraocular movement, facial paresis), tremor, vertigo, memory loss, paresthesia, peripheral neuropathy, peripheral nerve palsy, anxiety, insomnia, depression.

Hypersensitivity Reactions: an apparent hypersensitivity syndrome has been reported rarely that has included one or more of the following features: anaphylaxis, angioedema, lupus erythematous-like syndrome, polymyalgia rheumatica, vasculitis, purpura, thrombocytopenia, leukopenia, hemolytic anemia, positive ANA, ESR increase, arthritis, arthralgia, urticaria, asthenia, photosensitivity, fever, chills, flushing, malaise, dyspnea, toxic epidermal necrolysis, erythema multiforme, including Stevens-Johnson syndrome.

Gastrointestinal: pancreatitis, hepatitis, including chronic active hepatitis, cholestatic jaundice, fatty change in liver; and rarely, cirrhosis, fulminant hepatic necrosis, and hepatoma; anorexia, vomiting.

Skin: alopecia.

Reproductive: gynecomastia, loss of libido, erectile dysfunction.

Eye: progression of cataracts (lens opacities), ophthalmoplegia.

Laboratory Abnormalities: elevated transaminases, alkaline phosphatase, and bilirubin; thyroid function abnormalities.

OVERDOSAGE: After oral administration of MEVACOR to mice, the median lethal dose observed was >15 g/m².

Five healthy human volunteers have received up to 200 mg of lovastatin as a single dose without clinically significant adverse experiences. A few cases of accidental overdosage have been reported; no patients had any specific symptoms, and all patients recovered without sequelae. The maximum dose taken was 5 to 6 g.

Until further experience is obtained, no specific treatment of overdosage with MEVACOR can be recommended.

The dialyzability of lovastatin and its metabolites in man is not known at present.

DOSAGE AND ADMINISTRATION: The patient should be placed on a standard cholesterol-lowering diet before receiving MEVACOR and should continue on this diet during treatment with MEVACOR. MEVACOR should be given with meals.

The recommended starting dose is 20 mg once a day given with the evening meal. The recommended dosing range is 20 to 80 mg/day in single or divided doses; the maximum recommended dose is 80 mg/day. Adjustments of dosage should be made at intervals of 4 weeks or more. Doses should be individualized according to the patient's response (see Tables I to IV under CLINICAL PHARMACOLOGY, *Clinical Studies* in the full Prescribing Information for dose-response results).

In patients taking immunosuppressive drugs concomitantly with lovastatin (see WARNINGS, *Skeletal Muscle*), therapy should begin with 10 mg of MEVACOR and should not exceed 20 mg/day.

Cholesterol levels should be monitored periodically, and consideration should be given to reducing the dosage of MEVACOR if cholesterol levels fall below the targeted range.

Dosage in Patients with Renal Insufficiency: In patients with severe renal insufficiency (creatinine clearance <30 mL/min), dosage increases above 20 mg/day should be carefully considered and, if deemed necessary, implemented cautiously (see CLINICAL PHARMACOLOGY in the full Prescribing Information and WARNINGS, *Skeletal Muscle*).

For more detailed information, consult your MSD Representative or see the Prescribing Information.

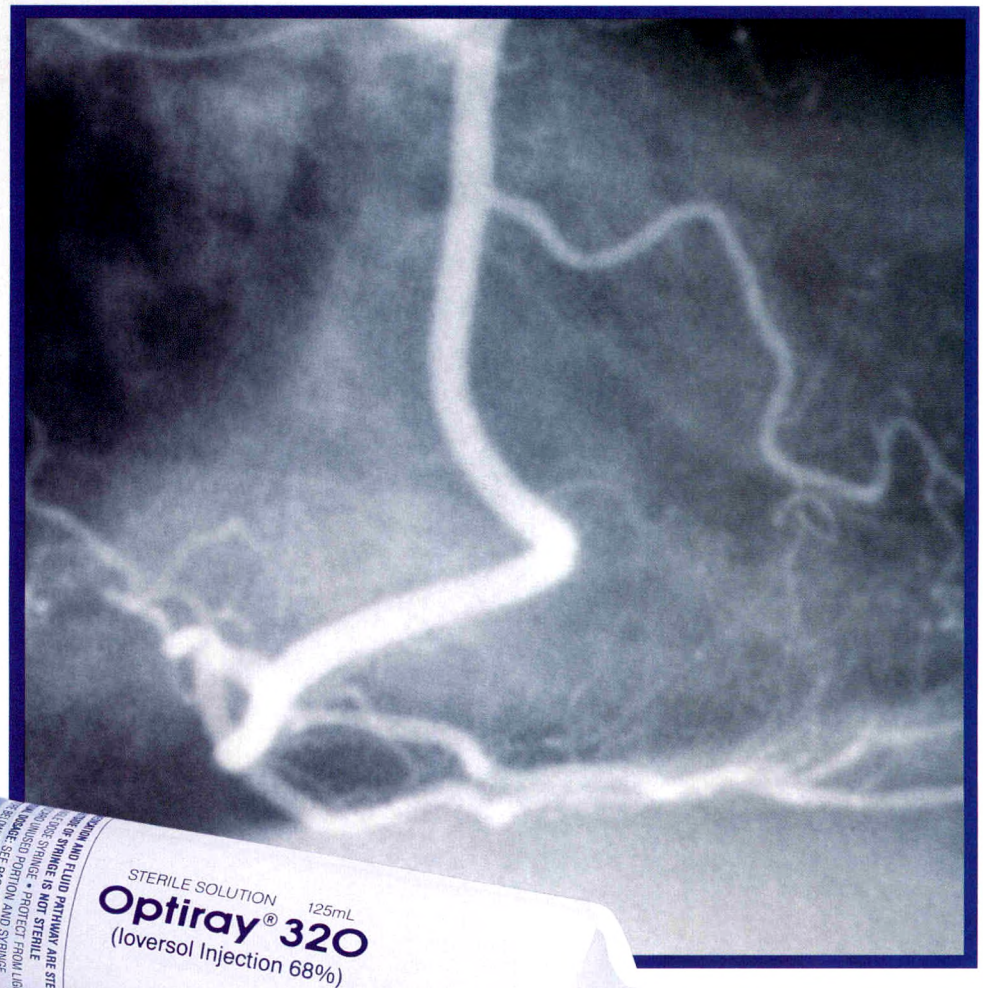
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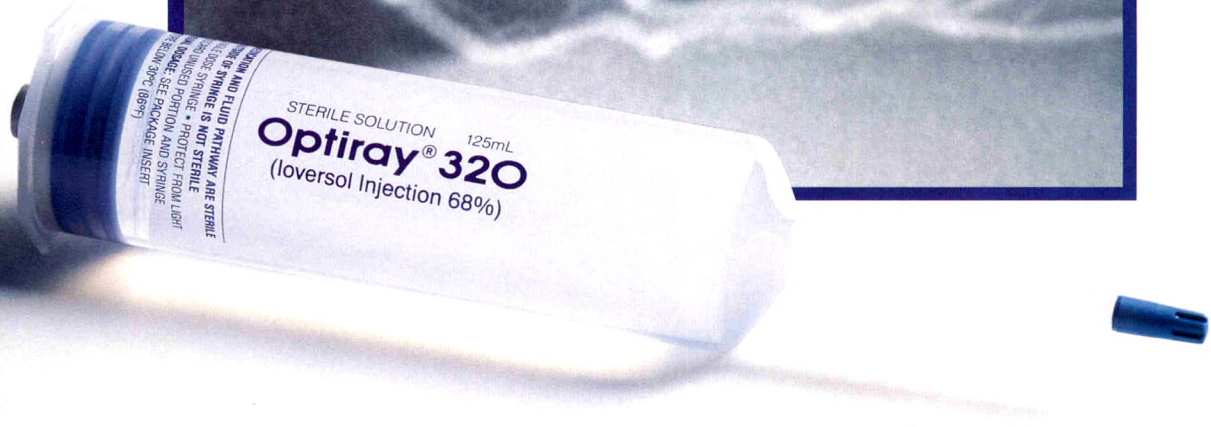
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There is a safer way
to get a great picture.
Nonionic
OPTIRAY®
(ioversol)

And a safer way to great cardiac imaging.



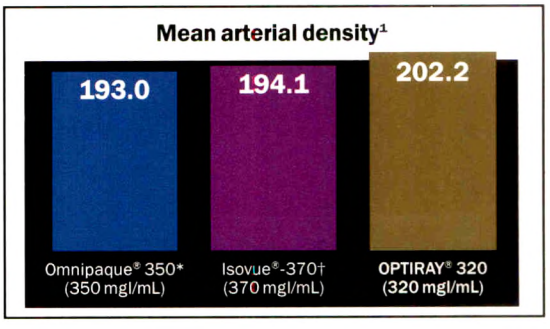


Also available in a 35% concentration: OPTIRAY® 350 (ioversol injection 74%)

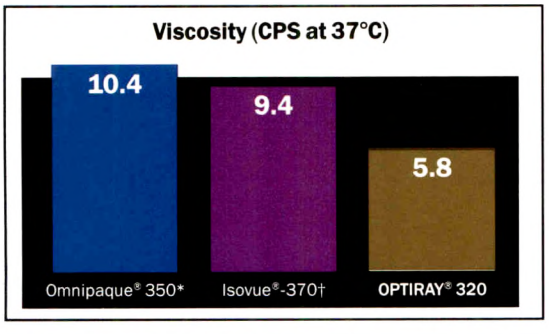
Great cardiac visualization with the safety of lower iodine...

A recent clinical study showed that OPTIRAY® 320 (ioversol injection 68%) provides equivalent image density when compared with contrast agents of higher iodine concentration.[1]

So OPTIRAY® 320 provides a means for reducing the amount of iodine administered with no reduction in overall image quality. And a lower iodine dose may reduce the likelihood of renal dysfunction.[2]

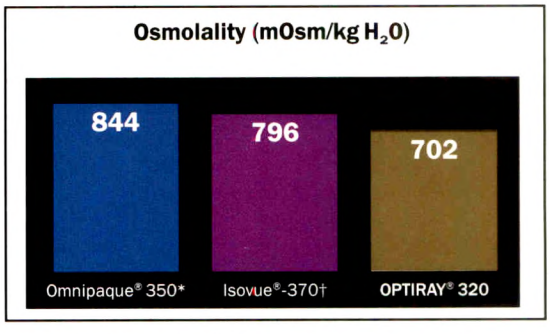


lower viscosity...



The low viscosity and greater flow rate of OPTIRAY® 320 mean easier hand injections and images equivalent to contrast agents with a higher iodine concentration.[1]

and lower osmolality.



OPTIRAY® 320 has the lowest osmolality of these nonionic contrast media.

Sometimes all you need is a little less, to get more.

All nonionic iodinated contrast media currently available inhibit blood coagulation, in vitro, less than ionic contrast media. Clotting has been reported when blood remains in contact with syringes containing nonionic contrast media. Therefore, meticulous intravascular administration technique is necessary to minimize thromboembolic events.

References:

1. Kern MJ, Roth RA, Aguirre FV, Beauman G, Vogel R. Effect of viscosity and iodine concentration of nonionic radiographic contrast media on coronary arteriography in patients. *Am Heart J.* 1992; 123:160-165. 2. Gomes AS, Baker JD, Martin-Paredero V, et al. Acute renal dysfunction after major arteriography. *AJR.* 1985; 145:1249-1253.

*Omnipaque® (iohexol) — Winthrop Pharmaceuticals
†Isovue® (iopamidol) — E.R. Squibb & Sons, Inc.

Please see the following page for a brief summary of prescribing information.

P24,213

Nonionic
OPTIRAY®
(ioversol)

A safer way to great imaging

OPTIRAY® 160 240 320 350 (Ioversol Injection)

DESCRIPTION: Each milliliter of OPTIRAY 160 (ioversol injection 34%) provides 339 mg of ioversol with 3.6 mg of tromethamine as a buffer and 0.2 mg of edetate calcium disodium as a stabilizer. OPTIRAY 160 provides 16% (160 mg/mL) organically bound iodine.

Each milliliter of OPTIRAY 240 (ioversol injection 51%) provides 509 mg of ioversol with 3.6 mg of tromethamine as a buffer and 0.2 mg of edetate calcium disodium as a stabilizer. OPTIRAY 240 provides 24% (240 mg/mL) organically bound iodine.

Each milliliter of OPTIRAY 320 (ioversol injection 68%) provides 678 mg of ioversol with 3.6 mg of tromethamine as a buffer and 0.2 mg of edetate calcium disodium as a stabilizer. OPTIRAY 320 provides 32% (320 mg/mL) organically bound iodine.

Each milliliter of OPTIRAY 350 (ioversol injection 74%) provides 741 mg of ioversol with 3.6 mg of tromethamine as a buffer and 0.2 mg of edetate calcium disodium as a stabilizer. OPTIRAY 350 provides 35% (350 mg/mL) organically bound iodine.

CONTRAINDICATIONS: None.

WARNINGS: Nonionic iodinated contrast media inhibit blood coagulation, in vitro, less than ionic contrast media. Clotting has been reported when blood remains in contact with syringes containing nonionic contrast media.

Serious, rarely fatal, thromboembolic events causing myocardial infarction and stroke have been reported during angiographic procedures with both ionic and nonionic contrast media. Therefore, meticulous intravascular administration technique is necessary, particularly during angiographic procedures, to minimize thromboembolic events. Numerous factors, including length of procedure, catheter and syringe material, underlying disease state and concomitant medications may contribute to the development of thromboembolic events. For these reasons, meticulous angiographic techniques are recommended including close attention to guidewire and catheter manipulation, use of manifold systems and/or three-way stopcocks, frequent catheter flushing with heparinized saline solutions and minimizing the length of the procedure. The use of plastic syringes in place of glass syringes has been reported to decrease but not eliminate the likelihood of in vitro clotting.

Serious or fatal reactions have been associated with the administration of iodine-containing radiopaque media. It is of utmost importance to be completely prepared to treat any contrast medium reaction.

As with any contrast medium, serious neurologic sequelae, including permanent paralysis, can occur following cerebral arteriography, selective spinal arteriography and arteriography of vessels supplying the spinal cord. A cause-effect relationship to the contrast medium has not been established since the patients' pre-existing condition and procedural technique are causative factors in themselves. The arterial injection of a contrast medium should never be made following the administration of vasopressors since they strongly potentiate neurologic effects.

Caution must be exercised in patients with severely impaired renal function, combined renal and hepatic disease, severe thyrotoxicosis, myelomatosis, or anuria, particularly when large doses are administered.

Intravascularly administered iodine-containing radiopaque media are potentially hazardous in patients with multiple myeloma or other paraproteinemia, particularly in those with therapeutically resistant anuria. Myeloma occurs most commonly in persons over age 40. Although neither the contrast agent nor dehydration has been proved separately to be the cause of anuria in myelomatous patients, it has been speculated that the combination of both may be causative. The risk in myelomatous patients is not a contraindication to the procedure; however, special precautions, including maintenance of normal hydration and close monitoring, are required. Partial dehydration in the preparation of these patients prior to injection is not recommended since this may predispose the patient to precipitation of the myeloma protein.

Administration of radiopaque materials to patients known or suspected of having pheochromocytoma should be performed with extreme caution. If, in the opinion of the physician, the possible benefits of such procedures outweigh the considered risks, the procedures may be performed; however, the amount of radiopaque medium injected should be kept to an absolute minimum. The blood pressure should be assessed throughout the procedure, and measures for treatment of a hypertensive crisis should be available.

Contrast media may promote sickling in individuals who are homozygous for sickle cell disease when administered intravascularly.

Reports of thyroid storm following the intravascular use of iodinated radiopaque agents in patients with hyperthyroidism or with an autonomously functioning thyroid nodule, suggest that this additional risk be evaluated in such patients before use of any contrast medium.

PRECAUTIONS: *General:* Diagnostic procedures which involve the use of iodinated intravascular contrast agents should be carried out under the direction of personnel skilled and experienced in the particular procedure to be performed. A fully equipped emergency cart, or equivalent supplies and equipment, and personnel competent in recognizing and treating adverse reactions of all types should always be available. Since severe delayed reactions have been known to occur, emergency facilities and competent personnel should be available for at least 30 to 60 minutes after administration.

Preparatory dehydration is dangerous and may contribute to acute renal failure in patients with advanced vascular disease, diabetic patients, and in susceptible non-diabetic patients (often elderly with pre-existing renal disease). *Patients should be well hydrated prior to and following the administration of OPTIRAY.*

The possibility of a reaction, including serious, life-threatening, fatal, anaphylactoid or cardiovascular reactions, should always be considered (See ADVERSE REACTIONS). Increased risk is associated with a history of previous reaction to a contrast medium, a known sensitivity to iodine and known allergies (i.e., bronchial asthma, hay fever and food allergies) or hypersensitivities.

The occurrence of severe idiosyncratic reactions has prompted the use of several pretesting methods. However, pretesting cannot be relied upon to predict severe reactions and may itself be hazardous to the patient. It is suggested that a thorough medical history with emphasis on allergy and hypersensitivity, prior to the injection of any contrast medium, may be more accurate than pretesting in predicting potential adverse reactions. A positive history of allergies or hypersensitivity does not arbitrarily contraindicate the use of a contrast agent when a diagnostic procedure is thought essential, but caution should be exercised. Premedication with antihistamines or corticosteroids to avoid or minimize possible allergic reactions in such patients should be considered. Reports indicate that such pretreatment does not prevent serious life-threatening reactions, but may reduce both their incidence and severity.

General anesthesia may be indicated in the performance of some procedures in selected patients; however, a higher incidence of adverse reactions has been reported in these patients, and may be attributable to the inability of the patient to identify untoward symptoms or to the hypotensive effect of anesthesia which can prolong the circulation time and increase the duration of exposure to the contrast agent.

In angiographic procedures, the possibility of dislodging plaques or damaging or perforating the vessel wall should be considered during catheter manipulations and contrast medium injection. Test injections to insure proper catheter placement are suggested.

Angiography should be avoided whenever possible in patients with homocystinuria because of the risk of inducing thrombosis and embolism.

Patients with congestive heart failure should be observed for several hours following the procedure to detect delayed hemodynamic disturbances which may be associated with a transitory increase in the circulating osmotic load.

Selective coronary arteriography should be performed only in selected patients and those in whom the expected benefits outweigh the procedural risk. The inherent risks of angiocardiography in patients with chronic pulmonary emphysema must be weighed against the necessity for performing this procedure.

Extreme caution during injection of a contrast medium is necessary to avoid extravasation. This is especially important in patients with severe arterial or venous disease.

Drug Interactions: Renal toxicity has been reported in a few patients with liver dysfunction who were given oral cholecystographic agents followed by intravascular contrast agents. Administration of any intravascular contrast agent should therefore be postponed in patients who have recently received a cholecystographic contrast agent.

Other drugs should not be mixed with ioversol injection.

Drug Laboratory Test Interactions: The results of PBI and radioactive iodine uptake studies, which depend on iodine estimation, will not accurately reflect thyroid function for up to 16 days following administration of iodinated contrast media. However, thyroid function tests not depending on iodine estimations, e.g., T3 resin uptake and total or free thyroxine (T4) assays are not affected.

Carcinogenesis, Mutagenesis, Impairment of Fertility: No long term animal studies have been performed to evaluate carcinogenic potential. However, animal studies suggest that this drug is not mutagenic and does not affect fertility.

Pregnancy Category B: No teratogenic effects attributable to ioversol have been observed in teratology studies performed in animals. There are, however, no adequate and well controlled studies in pregnant women. It is not known whether ioversol crosses the placental barrier or reaches fetal tissues. However, many injectable contrast agents cross the placental barrier in humans and appear to enter fetal tissue passively. Because animal teratology studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed. X-ray procedures involve a certain risk related to the exposure of the fetus.

Nursing Mothers: It is not known whether ioversol is excreted in human milk. However, many injectable contrast agents are excreted unchanged in human milk. Although it has not been established that serious adverse reactions occur in nursing infants, caution should be exercised when intravascular contrast media are administered to nursing women because of potential adverse reactions, and consideration should be given to temporarily discontinuing nursing.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: Adverse reactions following the use of OPTIRAY formulations are usually mild to moderate, of short duration and resolve spontaneously (without treatment). However, serious, life-threatening and fatal reactions, mostly of cardiovascular origin, have been associated with the administration of iodine-containing contrast media.

Injections of contrast media are often associated with sensations of warmth and pain. In controlled double-blind clinical studies, significantly less warmth and pain were associated with the injection of OPTIRAY than with iothalamate meglumine, diatrizoate meglumine, and diatrizoate meglumine and diatrizoate sodium.

When OPTIRAY was used for coronary arteriography and ventriculography in double-blind clinical trials, electrocardiographic and hemodynamic changes occurred with less frequency and severity with ioversol injection than with diatrizoate meglumine and diatrizoate sodium.

Following coronary artery and left ventricular injection, electrocardiographic parameters were affected less with OPTIRAY (ioversol injection) than with diatrizoate meglumine and diatrizoate sodium injection. These parameters included the following: bradycardia, tachycardia, T-wave amplitude, ST depression and ST elevation.

OPTIRAY has also been shown to cause fewer changes in cardiac function and systemic blood pressure than conventional ionic media. These include cardiac output, left ventricular systolic and end-diastolic pressure, right ventricular systolic and pulmonary artery systolic pressures and decreases in systolic and diastolic blood pressures.

The following table of incidence of reactions is based upon clinical trials with OPTIRAY formulations in over 1466 patients. This listing includes all adverse reactions which were coincidental to the administration of ioversol regardless of their direct attributability to the drug or the procedure. Adverse reactions are listed by organ system and in decreasing order of occurrence. Significantly more severe reactions are listed before others in a system regardless of frequency.

Adverse Reactions

System	> 1%	≤ 1%
Cardiovascular	none	angina pectoris hypotension blood pressure fluctuation arterial spasm bradycardia conduction defect false aneurysm hypertension transient arrhythmia vascular trauma
Digestive	none	nausea vomiting
Nervous	none	cerebral infarct headache blurred vision vertigo lightheadedness vasovagal reaction disorientation paresthesia dysphasia muscle spasm syncope visual hallucination
Respiratory	none	laryngeal edema pulmonary edema sneezing nasal congestion coughing shortness of breath hypoxia
Skin	none	periorbital edema urticaria facial edema flush pruritus
Miscellaneous	none	extravasation hematoma shaking chills bad taste general pain

Regardless of the contrast medium employed, the overall incidence of serious adverse reaction is higher with coronary arteriography than with other procedures. Cardiac decompensation, serious arrhythmias, myocardial ischemia or myocardial infarction may occur during coronary arteriography and left ventriculography.

General Adverse Reactions to Contrast Media

The following adverse reactions are possible with any parenterally administered iodinated contrast medium. Severe life-threatening reactions and fatalities, mostly of cardiovascular origin, have occurred. Most deaths occur during injection or 5 to 10 minutes later; the main feature being cardiac arrest with cardiovascular disease as the main aggravating factor. Isolated reports of hypotensive collapse and shock are found in the literature. Based upon clinical literature, reported deaths from the administration of conventional iodinated contrast agents range from 6.6 per 1 million (0.00066 percent) to 1 in 10,000 patients (0.01 percent).

The reported incidence of adverse reactions to contrast media in patients with a history of allergy is twice that of the general population. Patients with a history of previous reactions to a contrast medium are three times more susceptible than other patients. However, sensitivity to contrast media does not appear to increase with repeated examinations.

Adverse reactions to injectable contrast media fall into two categories: chemotoxic reactions and idiosyncratic reactions.

Chemotoxic reactions result from the physicochemical properties of the contrast medium, the dose and the speed of injection. All hemodynamic disturbances and injuries to organs or vessels perfused by the contrast medium are included in this category.

Idiosyncratic reactions include all other reactions. They occur more frequently in patients 20 to 40 years old. Idiosyncratic reactions may or may not be dependent on the dose injected, the speed of injection, the mode of injection and the radiographic procedure. Idiosyncratic reactions are subdivided into minor, intermediate and severe. The minor reactions are self-limited and of short duration; the severe reactions are life-threatening and treatment is urgent and mandatory.

In addition to the adverse reactions reported for ioversol, the following additional adverse reactions have been reported with the use of other contrast agents and are possible with any water soluble, iodinated contrast agent.

Nervous: convulsions, aphasia, paralysis, visual field losses which are usually transient but may be permanent, coma and death.

Cardiovascular: angioneurotic edema, peripheral edema, vasodilation, thrombosis and rarely thrombophlebitis, disseminated intravascular coagulation and shock.

Skin: maculopapular rash, erythema, conjunctival symptoms, ecchymosis and tissue necrosis.

Respiratory: choking, dyspnea, wheezing which may be an initial manifestation of more severe and infrequent reactions including asthmatic attack, laryngospasm and bronchospasm, apnea and cyanosis. Rarely these allergic-type reactions can progress into anaphylaxis with loss of consciousness, coma, severe cardiovascular disturbances and death.

Miscellaneous: hyperthermia, temporary anuria or other nephropathy.

Other reactions may also occur with the use of any contrast agent as a consequence of the procedural hazard; these include hemorrhage or pseudoaneurysms at the puncture site, brachial plexus palsy following axillary artery injections, chest pain, myocardial infarction, and transient changes in hepatorenal chemistry tests. Arterial thrombosis, displacement of arterial plaques, venous thrombosis, dissection of the coronary vessels and transient sinus arrest are rare complications.

In cerebral arteriography, cardiovascular reactions that may occur with some frequency are bradycardia and either an increase or decrease in systemic blood pressure. Neurological reactions that may occur are: seizures, drowsiness, transient paresis, and mild disturbances in vision.

Central nervous system reactions with OPTIRAY in controlled clinical studies in cerebral arteriography that were considered drug-related and occurred with frequencies greater than 1% were: headache, bradycardia, blood pressure fluctuation, disorientation, nausea and vertigo.

In aortography, depending on the technique employed, the risks of this procedure also include the following: injury to the aorta and neighboring organs, pleural puncture, renal damage including infarction and acute tubular necrosis with oliguria and anuria, retroperitoneal hemorrhage from the translumbar approach and spinal cord injury and pathology associated with the syndrome of transverse myelitis. Under conditions of slowed aortic circulation there is an increased likelihood for aortography to cause muscle spasm. Occasional serious neurologic complications, including paraplegia, have also been reported in patients with aortoiliac obstruction, femoral artery obstruction, abdominal compression, hypotension, hypertension, spinal anesthesia, and injection of vasopressors to increase contrast. In these patients the concentration, volume, and number of repeat injections of the medium should be maintained at a minimum with appropriate intervals between injections. The position of the patient and catheter tip should be carefully monitored.

Entry of a large aortic dose into the renal artery may cause, even in the absence of symptoms, albuminuria, hematuria, and an elevated creatinine and urea nitrogen. Rapid and complete return of function usually follows.

There were no cardiovascular system reactions with OPTIRAY in controlled clinical studies in coronary arteriography with left ventriculography that were considered drug-related and occurred with a frequency greater than 1%.

PRECAUTIONS FOR SPECIFIC PROCEDURES:

Cerebral Arteriography

Extreme caution is advised in patients with advanced arteriosclerosis, severe hypertension, cardiac decompensation, senility, recent cerebral thrombosis or embolism, and migraine.

Peripheral Arteriography

Pulsation should be present in the artery to be injected. In thromboangiitis obliterans, or ascending infection associated with severe ischemia, angiography should be performed with extreme caution, if at all.

Coronary Arteriography and Left Ventriculography

Mandatory prerequisites to the procedure are specialized personnel, ECG monitoring apparatus and adequate facilities for immediate resuscitation and cardioversion. Electrocardiograms and vital signs should be routinely monitored throughout the procedure.

Venography

Special care is required when venography is performed in patients with suspected thrombosis, phlebitis, severe ischemic disease, local infection or a totally obstructed venous system. In order to minimize extravasation during injection, fluoroscopy is recommended.

Intravenous Digital Subtraction Angiography

In addition to the general precautions previously described, the risks associated with IV DSA include those usually attendant with catheter procedures and include intramural injections, vessel dissection and tissue extravasation. The potential risk is reduced when small test injections of contrast medium are made under fluoroscopic observation to insure that the catheter tip is properly positioned and, in the case of peripheral placement, that the vein is of adequate size.

Patient motion, including respiration and swallowing, can result in misregistration leading to image degradation and non-diagnostic studies.

OVERDOSAGE: The adverse effects of overdosage are life-threatening and affect mainly the pulmonary and cardiovascular system. Treatment of an overdosage is directed toward the support of all vital functions, and prompt institution of symptomatic therapy.

Ioversol does not bind to plasma or serum protein and is therefore, dialyzable.

The intravenous LD_{50} values (gI/kg) for ioversol in animals were: 17 (mice), and 15 (rats).

DOSAGE AND ADMINISTRATION: Details on dosage are provided in the package insert. CONSULT FULL PACKAGE INSERT BEFORE USE.

MALLINCKRODT *Cardiology*

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1399

Beneficial Effect of Amiodarone on Cardiac Mortality in Patients with Asymptomatic Complex Ventricular Arrhythmias After Acute Myocardial Infarction and Preserved But Not Impaired Left Ventricular Function

Matthias Pfisterer, Wolfgang Kiowski, Dieter Burckhardt, Ferenc Follath, and Felix Burkart

To determine whether the beneficial effect of low-dose amiodarone on survival in patients with complex ventricular arrhythmias after myocardial infarction was dependent on left ventricular (LV) function, results of the Basel Antiarrhythmic Study of Infarct Survival were analyzed. With LV ejection fraction ≥40% at baseline, there was a significantly lower 1-year mortality and fewer arrhythmic events in patients taking amiodarone versus control subjects ($p < 0.03$ each); this was not the case for patients with LV ejection fraction <40%. Although this report deals with a subanalysis and relatively small patient groups, it suggests that a beneficial effect of amiodarone on survival after myocardial infarction may be small or absent in presence of LV dysfunction, a finding that should be addressed for ongoing and future larger studies with this drug.

1403

Incidence and Timing of Recurrences of Sudden Death and Ventricular Tachycardia During Antiarrhythmic Drug Treatment After Myocardial Infarction

Luz Maria Rodriguez, Joep Smeets, Gilles E. O'Hara, Peter Geelen, Pedro Brugada, and Hein J. J. Wellens

Incidence and timing of recurrences of sustained ventricular tachycardia (VT) or sudden death were studied in 206 patients who survived their first episode of ventricular fibrillation (n = 52) or sustained VT (n = 154) after myocardial infarction. All patients were treated with (empirically selected) antiarrhythmic drugs; 49% received amiodarone. Incidence of sudden death had 2 peaks at approximately 3 and 12 months. Nonfatal VT recurrences were more frequent (most often occurring in first 6 months) in the VT than in the ventricular fibrillation group. Sudden death occurred during the following 3 years in only 10% of patients who survived 1 year. There was a much higher incidence of sudden death in patients with left ventricular ejection fraction (LVEF) ≤40% than in those with LVEF >40% (28 of 65 vs 3 of 141; $p < 0.0001$), but no relation between LVEF and nonfatal VT recurrences.

1407

Usefulness of Pirenzepine, an M_1 Antimuscarinic Agent, for Effort Myocardial Ischemia

Paolo Marraccini, Enrico Orsini, Guido Nassi, Claudio Michelassi, and Antonio L'Abbate

This study evaluated the effect of pirenzepine, an M_1 antimuscarinic agent, on exercise duration and ischemic threshold in patients with angiographically documented coronary artery disease. Twenty-five patients underwent 3 randomized multistage bicycle exercise stress tests after intravenous administration of saline (2 ml), isosorbide-dinitrate (1 mg) and pirenzepine (2 mg). Compared with saline, both pirenzepine and

isosorbide dinitrate significantly improved time to ischemia (0.15 mV ST-segment depression) from 6.5 ± 1.9 to 7.8 ± 1.8 and 8.6 ± 1.9 minutes, and rate-pressure product at ischemia from 21,498 ± 4,903 to 24,083 ± 6,692 and 24,547 ± 5,390 mm Hg · beats/min, respectively. Moreover, compared with saline, pirenzepine decreased resting heart rate from 71 ± 9 to 60 ± 11 beats/min ($p < 0.01$), and induced a significant increment of heart rate at ischemia from 117 ± 18 to 126 ± 21 beats/min ($p < 0.05$). Thus, if the results of this study were to be confirmed, the M_1 antimuscarinic agents could be considered as a new alternative treatment for effort myocardial ischemia.

1412

Simultaneous Transesophageal Two-Dimensional Echocardiography and Atrial Pacing for Detecting Coronary Artery Disease

Otto Kamp, Carel C. de Cock, Albert J. Funke Küpper, Jan P. Roos, and Cees A. Visser

A new technique is described for the assessment of coronary artery disease (CAD), combining transesophageal 2-dimensional echocardiography and transesophageal atrial pacing. This technique was successfully used in 70 of 71 patients, and had a sensitivity of 83% and a specificity of 94% for assessment of CAD. In patients with previous myocardial infarction, sensitivity and specificity for detection of multivessel disease was 77 and 100%. Exercise electrocardiography and simultaneous 12-lead electrocardiography during atrial pacing had a sensitivity of 50 and 52%, respectively. It is concluded that this alternative technique is feasible and promising for assessing CAD, with a higher sensitivity and specificity than exercise and simultaneous 12-lead electrocardiography.

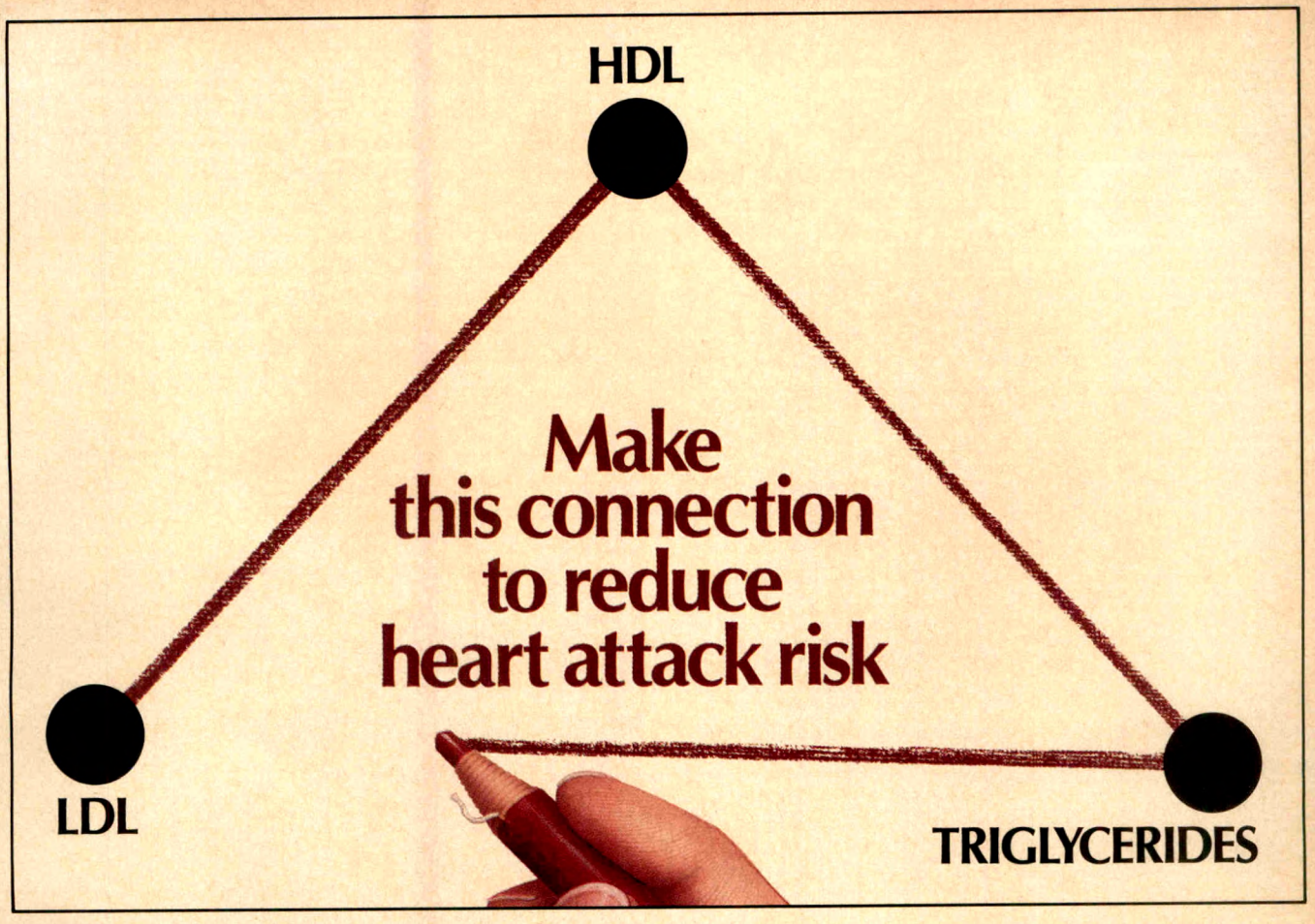
1417

Outcome After Prolonged Balloon Inflations of >20 Minutes for Initially Unsuccessful Percutaneous Transluminal Coronary Angioplasty

John D. Jackman, Jr., James P. Zidar, James E. Tcheng, Amy B. Overman, Harry R. Phillips, and Richard S. Stack

A strategy of prolonged balloon inflations of >20 minutes was assessed in 40 patients with unsuccessful percutaneous transluminal coronary angioplasty (PTCA) despite extensive previous inflations. After an average longest inflation of 11 minutes and an average total inflation time of 17 minutes, these patients with initially unsuccessful PTCA received prolonged balloon inflation averaging 30 minutes. Lesion stenosis was reduced from 91 ± 9 to 68 ± 16% by initial efforts and then to 47 ± 16% after prolonged balloon inflation ($p = 0.0001$ vs before prolonged inflation). Procedural success occurred in 32 patients (80%). Coronary bypass grafting became necessary in 8 patients (20%) of the entire cohort in hospital. Prolonged balloon inflations of >20 minutes are successful in 80% of patients in whom initial extensive inflations were not. Prolonged balloon inflations may thus be desirable before consideration of bypass grafting or stenting.

Continued on page A31



LOPID® BID

(gemfibrozil) 600-mg Tablets

Reduced the incidence of heart attack* 71%

—in a high-risk subgroup of Helsinki Heart Study (HHS) patients with a triad of lipid disorders: coexisting low HDL, high triglycerides, and high LDL. While the overall reduction in heart attack in the HHS was 34%, the greatest reduction was achieved among these LOPID patients with baseline triglycerides >200 mg/dL and baseline LDL/HDL ratio >5 (n = 154).†[1]

TREATS THE ENTIRE TRIAD
DRAMATICALLY REDUCES HEART ATTACK

LOPID is indicated for reducing the risk of developing coronary heart disease **only** in type IIb patients without history or symptoms of existing coronary heart disease, who have had an inadequate response to weight loss, diet, exercise, and other pharmacologic agents (such as bile acid sequestrants and nicotinic acid) and who have the following triad of lipid abnormalities: low HDL in addition to elevated LDL and triglycerides. LOPID is not indicated for the treatment of patients with low HDL as their only lipid abnormality.

Contraindicated in patients with hepatic or severe renal dysfunction, including primary biliary cirrhosis, preexisting gallbladder disease, or hypersensitivity to gemfibrozil. LOPID may increase cholesterol secretion into the bile, leading to cholelithiasis. Caution should be exercised when anticoagulants are given in conjunction with LOPID.

Please see adjacent page of this advertisement for warnings, contraindications, and brief summary of prescribing information.

*Defined as a combination of definite coronary death and/or definite myocardial infarction.

†Mean HDL = 35 mg/dL; mean LDL = 208 mg/dL; P = .005; 95% CI 21.2 to 118.6.

Reference 1. Manninen V, Tenkanen L, Koskinen P, et al. Joint effects of serum triglyceride and LDL cholesterol and HDL cholesterol concentrations on coronary heart disease risk in the Helsinki Heart Study: implications for treatment. *Circulation.* 1992;85:37-45.

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PARKE-DAVIS

BOOTS PHARMACEUTICALS

Before prescribing, please see full prescribing information. A Brief Summary follows.

CONTRAINDICATIONS

1. Hepatic or severe renal dysfunction, including primary biliary cirrhosis.
2. Preexisting gallbladder disease (see WARNINGS).
3. Hypersensitivity to gemfibrozil.

WARNINGS

1. Because of chemical, pharmacological, and clinical similarities between gemfibrozil and clofibrate, the adverse findings with clofibrate in two large clinical studies may also apply to gemfibrozil. In the first of those studies, the Coronary Drug Project, 1000 subjects with previous myocardial infarction were treated for five years with clofibrate. There was no difference in mortality between the clofibrate-treated subjects and 3000 placebo-treated subjects, but twice as many clofibrate-treated subjects developed cholelithiasis and cholecystitis requiring surgery. In the other study, conducted by the World Health Organization (WHO), 5000 subjects without known coronary heart disease were treated with clofibrate for five years and followed one year beyond. There was a statistically significant, 44%, higher age-adjusted total mortality in the clofibrate-treated than in a comparable placebo-treated control group during the trial period. The excess mortality was due to a 33% increase in noncardiovascular causes, including malignancy, post-cholecystectomy complications, and pancreatitis. The higher risk of clofibrate-treated subjects for gallbladder disease was confirmed.

Because of the more limited size of the Helsinki Heart Study, the observed difference in mortality from any cause between the Lopid and placebo group is not statistically significantly different from the 29% excess mortality reported in the clofibrate group in the separate WHO study at the 9 year follow-up (see CLINICAL PHARMACOLOGY). Noncoronary heart disease related mortality showed an excess in the group originally randomized to Lopid primarily due to cancer deaths observed during the open-label extension.

During the 5 year primary prevention component of the Helsinki Heart Study mortality from any cause was 44 (2.2%) in the Lopid group and 43 (2.1%) in the placebo group; including the 3.5 year follow-up period since the trial was completed, cumulative mortality from any cause was 101 (4.9%) in the Lopid group and 83 (4.1%) in the group originally randomized to placebo (hazard ratio 1.20 in favor of placebo). Because of the more limited size of the Helsinki Heart Study, the observed difference in mortality from any cause between the Lopid and placebo groups at year-5 or at year-8.5 is not statistically significantly different from the 29% excess mortality reported in the clofibrate group in the separate WHO study at the 9 year follow-up. Noncoronary heart disease related mortality showed an excess in the group originally randomized to Lopid at the 8.5 year follow-up (65 Lopid versus 45 placebo noncoronary deaths).

The incidence of cancer (excluding basal cell carcinoma) discovered during the trial and in the 3.5 years after the trial was completed was 51 (2.5%) in both originally randomized groups. In addition, there were 16 basal cell carcinomas in the group originally randomized to Lopid and 9 in the group originally randomized to placebo ($p = 0.22$). There were 30 (1.5%) deaths attributed to cancer in the group originally randomized to Lopid and 18 (0.9%) in the group originally randomized to placebo ($p = 0.11$). Adverse outcomes, including coronary events, were higher in gemfibrozil patients in a corresponding study in men with a history of known or suspected coronary heart disease in the secondary prevention component of the Helsinki Heart Study. (See CLINICAL PHARMACOLOGY.)

2. A gallstone prevalence substudy of 450 Helsinki Heart Study participants showed a trend toward a greater prevalence of gallstones during the study within the Lopid treatment group (7.5% vs 4.9% for the placebo group, a 55% excess for the gemfibrozil group). A trend toward a greater incidence of gallbladder surgery was observed for the Lopid group (17 vs 11 subjects, a 54% excess). This result did not differ statistically from the increased incidence of cholecystectomy observed in the WHO study in the group treated with clofibrate. Both clofibrate and gemfibrozil may increase cholesterol excretion into the bile leading to cholelithiasis. If cholelithiasis is suspected, gallbladder studies are indicated. Lopid therapy should be discontinued if gallstones are found.

3. Since a reduction of mortality from coronary heart disease has not been demonstrated and because liver and interstitial cell testicular tumors were increased in rats, Lopid should be administered only to those patients described in the INDICATIONS AND USAGE section. If a significant serum lipid response is not obtained, Lopid should be discontinued.

4. Concomitant Anticoagulants – Caution should be exercised when anticoagulants are given in conjunction with Lopid. The dosage of the anticoagulant should be reduced to maintain the prothrombin time at the desired level to prevent bleeding complications. Frequent prothrombin determinations are advisable until it has been definitely determined that the prothrombin level has stabilized.

5. Concomitant therapy with Lopid and Mevacor® (lovastatin) has been associated with rhabdomyolysis, markedly elevated creatine kinase (CK) levels and myoglobinuria, leading in a high proportion of cases to acute renal failure. IN VIRTUALLY ALL PATIENTS WHO HAVE HAD AN UNSATISFACTORY LIPID RESPONSE TO EITHER DRUG ALONE, ANY POTENTIAL LIPID BENEFIT OF COMBINED THERAPY WITH LOVASTATIN AND GEMFIBROZIL DOES NOT OUTWEIGH THE RISKS OF SEVERE MYOPATHY, RHABDOMYOLYSIS, AND ACUTE RENAL FAILURE (see Drug Interactions). The use of fibrates alone, including Lopid, may occasionally be associated with myositis. Patients receiving Lopid and complaining of muscle pain, tenderness, or weakness should have prompt medical evaluation for myositis, including serum creatine kinase level determination. If myositis is suspected or diagnosed, Lopid therapy should be withdrawn.

6. Cataracts – Subcapsular bilateral cataracts occurred in 10%, and unilateral in 6.3% of male rats treated with gemfibrozil at 10 times the human dose.

PRECAUTIONS

1. **Initial Therapy** – Laboratory studies should be done to ascertain that the lipid levels are consistently abnormal. Before instituting Lopid therapy, every attempt should be made to control serum lipids with appropriate diet, exercise, weight loss in obese patients, and control of any medical problems such as diabetes mellitus and hypothyroidism that are contributing to the lipid abnormalities.

2. **Continued Therapy** – Periodic determination of serum lipids should be obtained, and the drug withdrawn if lipid response is inadequate after 3 months of therapy.

3. **Drug Interactions** – (A) **HMG-CoA reductase inhibitors:** Rhabdomyolysis has occurred with combined gemfibrozil and lovastatin therapy. It may be seen as early as 3 weeks after initiation of combined therapy or after several months. In most subjects who have had an unsatisfactory lipid response to either drug alone, the possible benefit of combined therapy with lovastatin (or other HMG-CoA reductase inhibitors) and gemfibrozil does not outweigh the risks of severe myopathy, rhabdomyolysis, and acute renal failure. There is no assurance that periodic monitoring of creatine kinase will prevent the occurrence of severe myopathy and kidney damage.

(B) **Anticoagulants:** CAUTION SHOULD BE EXERCISED WHEN ANTICOAGULANTS ARE GIVEN IN CONJUNCTION WITH LOPID. THE DOSAGE OF THE ANTICOAGULANT SHOULD BE REDUCED TO MAINTAIN THE PROTHROMBIN TIME AT THE DESIRED LEVEL TO PREVENT BLEEDING COMPLICATIONS. FREQUENT PROTHROMBIN DETERMINATIONS ARE ADVISABLE UNTIL IT HAS BEEN DEFINITELY DETERMINED THAT THE PROTHROMBIN LEVEL HAS STABILIZED.

4. **Carcinogenesis, Mutagenesis, Impairment of Fertility** – Long-term studies have been conducted in rats at 0.2 and 2 times the human dose (based on surface area, mg/meter^2). The incidence of benign liver nodules and liver carcinomas was significantly increased in high dose male rats. The incidence of liver carcinomas increased also in low dose males, but this increase was not statistically significant ($p = 0.1$). Male rats had a dose-related and statistically significant increase of benign Leydig cell tumors. The higher dose female rats had a significant increase in the combined incidence of benign, and malignant liver neoplasms.

Long-term studies have been conducted in mice at 0.1 and 1 times the human dose (based on surface area). There were no statistically significant differences from controls in the incidence of liver tumors, but the doses tested were lower than those shown to be carcinogenic with other fibrates.

Electron microscopy studies have demonstrated a florid hepatic peroxisome proliferation following Lopid administration to the male rat. An adequate study to test for peroxisome proliferation has not been done in humans but changes in peroxisome morphology have been observed. Peroxisome proliferation has been shown to occur in humans with either of two other drugs of the fibrate class when liver biopsies were compared before and after treatment in the same individual.

Administration of approximately 0.6 and 2 times the human dose (based on surface area) to male rats for 10 weeks resulted in a dose-related decrease of fertility. Subsequent studies demonstrated that this effect was reversed after a drug-free period of about eight weeks, and it was not transmitted to the offspring.

5. **Pregnancy Category C** – Lopid has been shown to produce adverse effects in rats and rabbits at doses between 0.5 and 3 times the human dose (based on surface area) but no developmental toxicity or teratogenicity among offspring of either species. There are no adequate and well-controlled studies in pregnant women. Lopid should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Administration of Lopid to female rats at 0.6 and 2 times the human dose (based on surface area) before and throughout gestation caused a dose-related decrease in conception rate and, at the high dose, an increase in stillborns and a slight reduction in pup weight during lactation. There were also dose-related increased skeletal variations. Anophthalmia occurred, but rarely.

Lopid® (Gemfibrozil Tablets)

Administration of 0.6 and 2 times the human dose (based on surface area) of Lopid to female rats from gestation day 15 through weaning caused dose-related decreases in birth weight and suppressions of pup growth during lactation.

Administration of 1 and 3 times the human dose (based on surface area) of Lopid to female rabbits during organogenesis caused a dose-related decrease in litter size and at the high dose, an increased incidence of parietal bone variations.

6. **Nursing Mothers** – It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for tumorigenicity shown for Lopid in animal studies, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

7. **Hematologic Changes** – Mild hemoglobin, hematocrit and white blood cell decreases have been observed in occasional patients following initiation of Lopid therapy. However, these levels stabilize during long-term administration. Rarely, severe anemia, leukopenia, thrombocytopenia, and bone marrow hypoplasia have been reported. Therefore, periodic blood counts are recommended during the first 12 months of Lopid administration.

8. **Liver Function** – Abnormal liver function tests have been observed occasionally during Lopid administration, including elevations of AST (SGOT), ALT (SGPT), LDH, bilirubin, and alkaline phosphatase. These are usually reversible when Lopid is discontinued. Therefore periodic liver function studies are recommended and Lopid therapy should be terminated if abnormalities persist.

9. **Kidney Function** – There have been reports of worsening renal insufficiency upon the addition of Lopid therapy in individuals with baseline plasma creatinine > 2.0 mg/dL. In such patients, the use of alternative therapy should be considered against the risks and benefits of a lower dose of Lopid.

10. **Use in Children** – Safety and efficacy in children and adolescents have not been established.

ADVERSE REACTIONS

In the double-blind controlled phase of the primary prevention component of the Helsinki Heart Study, 2046 patients received Lopid for up to 5 years. In that study, the following adverse reactions were statistically more frequent in subjects in the Lopid group:

	LOPID (N=2046)	PLACEBO (N=2035)
	Frequency in percent of subjects	
Gastrointestinal reactions	34.2	23.8
Dyspepsia	19.6	11.9
Abdominal pain	9.8	5.6
Acute appendicitis (histologically confirmed in most cases where data were available)	1.2	0.6
Atrial fibrillation	0.7	0.1
Adverse events reported by more than 1% of subjects, but without a significant difference between groups:		
Diarrhea	7.2	6.5
Fatigue	3.8	3.5
Nausea/Vomiting	2.5	2.1
Eczema	1.9	1.2
Rash	1.7	1.3
Vertigo	1.5	1.3
Constipation	1.4	1.3
Headache	1.2	1.1

Gallbladder surgery was performed in 0.9% of Lopid and 0.5% of placebo subjects in the primary prevention component, a 64% excess, which is not statistically different from the excess of gallbladder surgery observed in the clofibrate compared to the placebo group of the WHO study. Gallbladder surgery was also performed more frequently in the Lopid group compared to placebo (1.9% vs. 0.3%, $p = 0.07$) in the secondary prevention component. A statistically significant increase in appendectomy in the gemfibrozil group was seen also in the secondary prevention component (6 on gemfibrozil vs. 0 on placebo, $p = 0.014$).

Nervous system and special senses adverse reactions were more common in the Lopid group. These included hypesthesia, paresthesias, and taste perversion. Other adverse reactions that were more common among Lopid treatment group subjects but where a causal relationship was not established include cataracts, peripheral vascular disease, and intracerebral hemorrhage.

From other studies it seems probable that Lopid is causally related to the occurrence of MUSCULOSKELETAL SYMPTOMS (see WARNINGS), and to ABNORMAL LIVER FUNCTION TESTS and HEMATOLOGIC CHANGES (see PRECAUTIONS).

Reports of viral and bacterial infections (common cold, cough, urinary tract infections) were more common in gemfibrozil treated patients in other controlled clinical trials of 805 patients. Additional adverse reactions that have been reported for gemfibrozil are listed below by system. These are categorized according to whether a causal relationship to treatment with Lopid is probable or not established:

CAUSAL RELATIONSHIP PROBABLE: *Gastrointestinal:* cholestatic jaundice; *Central Nervous System:* dizziness, somnolence, paresthesia, peripheral neuritis, decreased libido, depression, headache; *Eye:* blurred vision; *Genitourinary:* impotence; *Musculoskeletal:* myopathy, myasthenia, myalgia, painful extremities, arthralgia, synovitis, rhabdomyolysis (see WARNINGS and Drug Interactions under PRECAUTIONS); *Clinical Laboratory:* increased creatine phosphokinase, increased bilirubin, increased liver transaminases (AST [SGOT], ALT [SGPT]), increased alkaline phosphatase; *Hematopoietic:* anemia, leukopenia, bone marrow hypoplasia, eosinophilia; *Immunologic:* angioedema, laryngeal edema, urticaria; *Integumentary:* exfoliative dermatitis, rash, dermatitis, pruritus.

CAUSAL RELATIONSHIP NOT ESTABLISHED: *General:* weight loss; *Cardiac:* extrasystoles; *Gastrointestinal:* pancreatitis, hepatoma, colitis; *Central Nervous System:* confusion, convulsions, syncope; *Eye:* retinal edema; *Genitourinary:* decreased male fertility, renal dysfunction; *Clinical Laboratory:* positive antinuclear antibody; *Hematopoietic:* thrombocytopenia; *Immunologic:* anaphylaxis, Lupus-like syndrome, vasculitis; *Integumentary:* alopecia.

DOSAGE AND ADMINISTRATION

The recommended dose for adults is 1200 mg administered in two divided doses 30 minutes before the morning and evening meal.

OVERDOSAGE

While there has been no reported case of overdosage, symptomatic supportive measures should be taken should it occur.

HOW SUPPLIED

Lopid (Tablet 737), white, elliptical, film-coated, scored tablets, each containing 600 mg gemfibrozil, are available as follows:

N 0071-0737-20 Bottles of 60
N 0071-0737-30 Bottles of 500
N 0071-0737-40 Unit dose packages of 100 (10 strips of 10 tablets each)
Parcode® No. 737

Storage: Store below 30° C (86° F).

REFERENCES

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4. Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol. *Arch Int Med* 1988;148:36-39.

Caution – Federal law prohibits dispensing without prescription.

0737G015

Revised April 1992

LOPID® BID
(gemfibrozil) 600-mg Tablets
RAISES HDL, LOWERS LDL AND TRIGLYCERIDES
DRAMATICALLY REDUCES HEART ATTACK

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A favorable side-effect profile[1]

Once-a-day dosing schedules result in improved compliance[2]

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Flexible dosage range

- Start with one 180-mg capsule daily
- Available in 180-, 240-, and 300-mg capsules

*Based on AWP prices.

Cardizem CD is indicated for the treatment of hypertension.

Please see brief summary of prescribing information on next page.

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(diltiazem HCl)

MARION MERRELL DOW INC.
PRESCRIPTION PRODUCTS DIVISION
KANSAS CITY, MO 64114

CCDAH087/A6672

6305C2

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(diltiazem HCl)

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- Start with one 180-mg capsule daily
- Monitor for 2 weeks
- If necessary, titrate to goal blood pressure

BRIEF SUMMARY

CARDIZEM® CD (diltiazem hydrochloride) Capsules

CARDIZEM® SR (diltiazem hydrochloride) Sustained Release Capsules

CONTRAINDICATIONS

CARDIZEM is contraindicated in (1) patients with sick sinus syndrome except in the presence of a functioning ventricular pacemaker, (2) patients with second- or third-degree AV block except in the presence of a functioning ventricular pacemaker, (3) patients with hypotension (less than 90 mm Hg systolic), (4) patients who have demonstrated hypersensitivity to the drug, and (5) patients with acute myocardial infarction and pulmonary congestion documented by X-ray on admission.

WARNINGS

1. Cardiac Conduction. CARDIZEM prolongs AV node refractory periods without significantly prolonging sinus node recovery time, except in patients with sick sinus syndrome. This effect may rarely result in abnormally slow heart rates (particularly in patients with sick sinus syndrome) or second- or third-degree AV block (13 of 3,007 patients or 0.43%). Concomitant use of diltiazem with beta-blockers or digitalis may result in additive effects on cardiac conduction. A patient with Prinzmetal's angina developed periods of asystole (2 to 5 seconds) after a single dose of 60 mg of diltiazem.

2. Congestive Heart Failure. Although diltiazem has a negative inotropic effect in isolated animal tissue preparations, hemodynamic studies in humans with normal ventricular function have not shown a reduction in cardiac index nor consistent negative effects on contractility (dp/dt). An acute study of oral diltiazem in patients with impaired ventricular function (ejection fraction 24% ± 6%) showed improvement in indices of ventricular function without significant decrease in contractile function (dp/dt). Worsening of congestive heart failure has been reported in patients with preexisting impairment of ventricular function. Experience with the use of CARDIZEM in combination with beta-blockers in patients with impaired ventricular function is limited. Caution should be exercised when using this combination.

3. Hypotension. Decreases in blood pressure associated with CARDIZEM therapy may occasionally result in symptomatic hypotension.

4. Acute Hepatic Injury. Mild elevations of transaminases with and without concomitant elevation in alkaline phosphatase and bilirubin have been observed in clinical studies. Such elevations were usually transient and frequently resolved even with continued diltiazem treatment. In rare instances, significant elevations in enzymes such as alkaline phosphatase, LDH, SGOT, SGPT, and other phenomena consistent with acute hepatic injury have been noted. These reactions tended to occur early after therapy initiation (1 to 8 weeks) and have been reversible upon discontinuation of drug therapy. The relationship to CARDIZEM is uncertain in some cases, but probable in some. (See PRECAUTIONS.)

PRECAUTIONS

General. CARDIZEM is extensively metabolized by the liver and excreted by the kidneys and in bile. As with any drug given over prolonged periods, laboratory parameters should be monitored at regular intervals. The drug should be used with caution in patients with impaired renal or hepatic function. In subacute and chronic dog and rat studies designed to produce toxicity, high doses of diltiazem were associated with hepatic damage. In special subacute hepatic studies, oral doses of 125 mg/kg and higher in rats were associated with histological changes in the liver which were reversible when the drug was discontinued. In dogs, doses of 20 mg/kg were also associated with hepatic changes; however, these changes were reversible with continued dosing.

Dermatological events (see ADVERSE REACTIONS section) may be transient and may disappear despite continued use of CARDIZEM. However, skin eruptions progressing to erythema multiforme and/or exfoliative dermatitis have also been infrequently reported. Should a dermatologic reaction persist, the drug should be discontinued.

Drug Interaction. Due to the potential for additive effects, caution and careful titration are warranted in patients receiving CARDIZEM concomitantly with any agents known to affect cardiac contractility and/or conduction. (See WARNINGS.) Pharmacologic studies indicate that there may be additive effects in prolonging AV conduction when using beta-blockers or digitalis concomitantly with CARDIZEM. (See WARNINGS.)

As with all drugs, care should be exercised when treating patients with multiple medications. CARDIZEM undergoes biotransformation by cytochrome P-450 mixed function oxidase. Coadministration of CARDIZEM with other agents which follow the same route of biotransformation may result in the competitive inhibition of metabolism. Dosages of similarly metabolized drugs such as cyclosporin, particularly those of low therapeutic ratio or in patients with renal and/or hepatic impairment, may require adjustment when starting or stopping concomitantly administered CARDIZEM to maintain optimum therapeutic blood levels.

Beta-blockers: Controlled and uncontrolled domestic studies suggest that concomitant use of CARDIZEM and beta-blockers is usually well tolerated, but available data are not sufficient to predict the effects of concomitant treatment in patients with left ventricular dysfunction or cardiac conduction abnormalities.

Administration of CARDIZEM (diltiazem hydrochloride) concomitantly with propranolol in five normal volunteers resulted in increased propranolol levels in all subjects and bioavailability of propranolol was increased approximately 50%. If combination therapy is initiated or withdrawn in conjunction with propranolol, an adjustment in the propranolol dose may be warranted. (See WARNINGS.)

Cimetidine: A study in six healthy volunteers has shown a significant increase in peak diltiazem plasma levels (58%) and area-under-the-curve (53%) after a 1-week course of cimetidine at 1,200 mg per day and diltiazem 60 mg per day. Ranitidine produced smaller, nonsignificant increases. The effect may be mediated by cimetidine's known inhibition of hepatic cytochrome P-450, the enzyme system probably responsible for the first-pass metabolism of diltiazem. Patients currently receiving diltiazem therapy should be carefully monitored for a change in pharmacological effect when initiating and discontinuing therapy with cimetidine. An adjustment in the diltiazem dose may be warranted.

Digitalis: Administration of CARDIZEM with digoxin in 24 healthy male subjects increased plasma digoxin concentrations approximately 20%. Another investigator found no increase in digoxin levels in 12 patients with coronary artery disease. Since there have been conflicting results regarding the effect of digoxin levels, it is recommended that digoxin levels be monitored when initiating, adjusting, and discontinuing CARDIZEM therapy to avoid possible over- or under-digitalization. (See WARNINGS.)

Anesthetics: The depression of cardiac contractility, conductivity, and automaticity as well as the vascular dilation associated with anesthetics may be potentiated by calcium channel blockers. When used concomitantly, anesthetics and calcium blockers should be titrated carefully.

Carcinogenesis, Mutagenesis, Impairment of Fertility. A 24-month study in rats at oral dosage levels of up to 100 mg/kg/day, and a 21-month study in mice at oral dosage levels of up to 30 mg/kg/day showed no evidence of carcinogenicity. There was also no mutagenic response in vitro or in vivo in mammalian cell assays or in vitro in bacteria. No evidence of impaired fertility was observed in a study performed in male and female rats at oral dosages of up to 100 mg/kg/day.

Pregnancy. Category C. Reproduction studies have been conducted in mice, rats, and rabbits. Administration of doses ranging from five to ten times greater (on a mg/kg basis) than the daily recommended therapeutic dose has resulted in embryo and fetal lethality. These doses, in some studies, have been reported to cause skeletal abnormalities. In the perinatal/postnatal studies, there was an increased incidence of stillbirths at doses of 20 times the human dose or greater.

There are no well-controlled studies in pregnant women; therefore, use CARDIZEM in pregnant women only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers. Diltiazem is excreted in human milk. One report suggests that concentrations in breast milk may approximate serum levels. If use of CARDIZEM is deemed essential, an alternative method of infant feeding should be instituted.

Pediatric Use. Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Serious adverse reactions have been rare in studies carried out to date, but it should be recognized that patients with impaired ventricular function and cardiac conduction abnormalities have usually been excluded from these studies.

The adverse events described below represent events observed in clinical studies of hypertensive patients receiving either CARDIZEM Tablets or CARDIZEM SR Capsules as well as experiences observed in studies of angina and during marketing. The most common events in hypertension studies are shown in a table with rates in placebo patients shown for comparison. Less common events are listed by body system; these include any adverse reactions seen in angina studies that were not observed in hypertension studies. In all hypertensive patients taking CARDIZEM Tablets or CARDIZEM SR Capsules studied (over 900), the most common adverse events were edema (9%), headache (8%), dizziness (6%), asthenia (5%), sinus bradycardia (3%), flushing (3%), and first-degree AV block (3%). Only edema and perhaps bradycardia and dizziness were dose related.

DOUBLE BLIND PLACEBO CONTROLLED HYPERTENSION TRIALS

ADVERSE	DILTIAZEM N=315 # PTS (%)	PLACEBO N=211 # PTS (%)
Headache	38 (12%)	17 (8%)
AV Block First Degree	24 (7.6%)	4 (1.9%)
Dizziness	22 (7%)	6 (2.8%)
Edema	19 (6%)	2 (0.9%)
Bradycardia	19 (6%)	3 (1.4%)
ECG Abnormality	13 (4.1%)	3 (1.4%)
Asthenia	10 (3.2%)	1 (0.5%)
Constipation	5 (1.6%)	2 (0.9%)
Dyspepsia	4 (1.3%)	1 (0.5%)
Nausea	4 (1.3%)	2 (0.9%)
Palpitations	4 (1.3%)	2 (0.9%)
Polyuria	4 (1.3%)	2 (0.9%)
Somnolence	4 (1.3%)	—
Alk Phos Increase	3 (1%)	1 (0.5%)
Hypotension	3 (1%)	1 (0.5%)
Insomnia	3 (1%)	1 (0.5%)
Rash	3 (1%)	1 (0.5%)
AV Block Second Degree	2 (0.6%)	—

The following table presents the most common adverse reactions reported in placebo-controlled trials in patients receiving CARDIZEM CD up to 360 mg with rates in placebo patients shown for comparison.

ADVERSE REACTION	CARDIZEM CD N=324	PLACEBO N=175
HEADACHE	9.0%	8.0%
BRADYCARDIA	4.3%	2.3%
EDEMA	3.7%	2.3%
DIZZINESS	3.1%	3.4%
ECG ABNORMALITY	3.1%	2.9%
AV BLOCK FIRST DEGREE	2.2%	—
ASTHENIA	1.9%	1.7%

In clinical trials of CARDIZEM CD Capsules, CARDIZEM Tablets, and CARDIZEM SR Capsules involving over 3000 patients, the most common events (ie, greater than 1%) were edema (4.9%), headache (4.9%), dizziness (3.5%), asthenia (2.7%), first-degree AV block (2.2%), bradycardia (1.6%), flushing (1.5%), nausea (1.4%), rash (1.3%), and dyspepsia (1.2%).

In addition, the following events were reported infrequently (less than 1%).

Cardiovascular: Angina, arrhythmia, AV block (second- or third-degree), bundle branch block, congestive heart failure, ECG abnormalities, hypotension, palpitations, syncope, tachycardia, ventricular extrasystoles.

Nervous System: Abnormal dreams, amnesia, depression, gait abnormality, hallucinations, insomnia, nervousness, paresthesia, personality change, somnolence, tinnitus, tremor.

Gastrointestinal: Anorexia, constipation, diarrhea, dry mouth, dysgeusia, mild elevations of SGOT, SGPT, LDH, and alkaline phosphatase (see hepatic warnings), thirst, vomiting, weight increase.

Dermatological: Petechiae, photosensitivity, pruritus, urticaria.

Other: Amblyopia, CPK increase, dyspnea, epistaxis, eye irritation, hyperglycemia, hyperuricemia, impotence, muscle cramps, nasal congestion, nocturia, osteoarticular pain, polyuria, sexual difficulties.

The following postmarketing events have been reported infrequently in patients receiving CARDIZEM: alopecia, erythema multiforme, exfoliative dermatitis, extrapyramidal symptoms, gingival hyperplasia, hemolytic anemia, increased bleeding time, leukopenia, purpura, retinopathy, and thrombocytopenia. In addition, events such as myocardial infarction have been observed which are not readily distinguishable from the natural history of the disease in these patients. A number of well-documented cases of generalized rash, characterized as leukocytoclastic vasculitis, have been reported. However, a definitive cause and effect relationship between these events and CARDIZEM therapy is yet to be established.

HOW SUPPLIED

CARDIZEM® CD (diltiazem hydrochloride) is available as capsules of 180 mg, 240 mg, and 300 mg in bottles of 30 and 90, and in UDIP® packages of 100.

CARDIZEM® SR (diltiazem hydrochloride) is available as sustained release capsules of 60 mg, 90 mg, and 120 mg in bottles of 100, and in UDIP® packages of 100.

CARDIZEM® CD Product Information as of October 1991
CARDIZEM® SR Product Information as of January 1991

References: **1.** Data on file, Marion Merrell Dow Inc. **2.** Cramer JA, Mattson RH, Prevey ML, et al. *JAMA.* 1989;261(22):3273-3274.

MARION MERRELL DOW INC.
PRESCRIPTION PRODUCTS DIVISION
KANSAS CITY, MO 64114

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1422
Referral Patterns and Exercise Response in the Rehabilitation of Female Coronary Patients Aged ≥62 Years
Philip A. Ades, Mary L. Waldmann, Donna M. Polk, and Janice T. Coflesky

Gender-related differences in cardiac rehabilitation referral patterns and response to an aerobic conditioning program were examined in 226 hospitalized older coronary patients (aged ≥62 years). Overall, cardiac rehabilitation participation rate was 21%. Older women were less likely to enter cardiac rehabilitation than were older men (15 vs 25%; $p = 0.06$), despite similar clinical profiles. This was primarily explained by a greater likelihood of primary physicians to strongly recommend cardiac rehabilitation to men. Before conditioning, women were less fit than were men; maximal oxygen consumption was 18% lower in women (16 ± 5 vs 20 ± 5 ml/kg/min; $p = 0.02$). However, both groups improved aerobic capacity similarly in response to a 12-week aerobic conditioning program, with maximal oxygen consumption increasing by 17% in women and by 19% in men. Thus, older female coronary patients are less likely to be referred for cardiac rehabilitation, despite a similar clinical profile and improvement in functional capacity from the training component.

1426
Amount of Exercise Necessary for the Patient with Coronary Artery Disease
Barry A. Franklin, Seymour Gordon, and Gerald C. Timmis

Exercise training appears to play an important role in the medical management of patients with coronary artery disease (CAD). The salutary effects of chronic exercise training are well documented. Low to moderate intensity exercise training can produce beneficial changes in aerobic capacity, cardiac function, coronary risk factors, psychosocial well-being, and possibly improve survival. There are, however, limitations to the benefits that exercise offers relative to the rehabilitation of patients with CAD. Contrary to the speculation of a few enthusiasts, regular exercise training, regardless of the frequency, intensity or duration, does not confer "immunity" to CAD or, for that matter, recurrent myocardial infarction. Unless future studies can show that the added benefits of excessive and/or high-intensity exercise outweigh the potential risks, it appears prudent to recommend more moderate exercise regimens for patients with CAD.

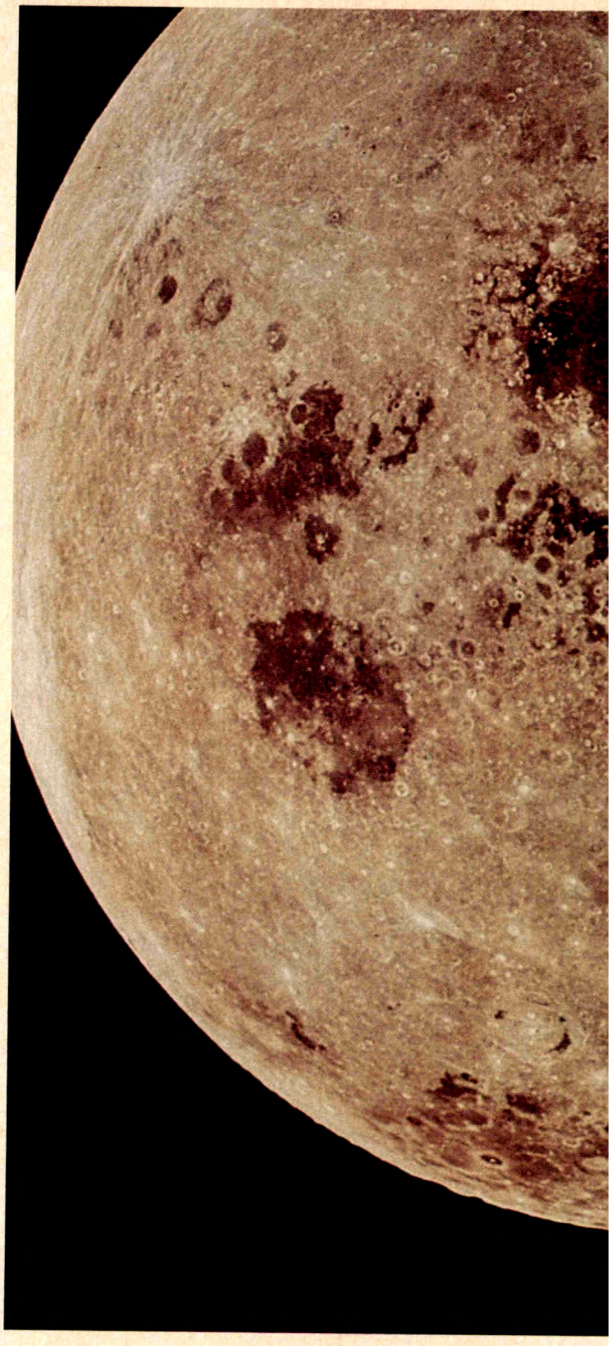
ARRHYTHMIAS AND CONDUCTION DISTURBANCES

1433
Effect of Direct, Reflex and Exercise-Provoked Increases in Sympathetic Tone on Idiopathic Ventricular Tachycardia
Michael G. Kienzle, James B. Martins, Luis Constantin, and Ann Aschoff

Sympathetic stimulation has a role in the occurrence and characteristics of ventricular tachycardia (VT) seen in patients without underlying coronary artery disease. The cardiovascular effects of exercise, isoproterenol infusion and orthostatic stress with lower body negative pressure were studied in a group of 11 patients with repetitive or sustained VT, and little or no cardiac disease. VT occurred spontaneously in only 2 patients with exer-

Continued on page A34

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cise, in 4 during orthostatic stress and in 2 during isoproterenol infusion. Programmed atrial or ventricular stimulation produced VT in 6 patients. Neither isoproterenol nor orthostatic stress consistently influenced VT duration, but both increased VT rate. It is concluded that there is considerable heterogeneity in arrhythmia responses to sympathetic augmentation in patients with VT unrelated to coronary artery disease.

SYSTEMIC HYPERTENSION

1439

Left Ventricular Function After Reversal of Myocardial Hypertrophy in Systemic Hypertension, and Response to Acute Increase of Afterload by Cold Pressor Test

Anna Maria Grandi, Achille Venco, Andrea Bertolini, Paolo Pantaleo, Daniela Corbellini, Guido Perani, Pietro Folino, Giuseppe Gobbi, and Giorgio Finardi

Using digitized M-mode echocardiography, the left ventricular (LV) response to acute increase in afterload was evaluated in 15 hypertensive patients by cold pressor test before and after regression of myocardial hypertrophy due to antihypertensive treatment with angiotensin-converting enzyme inhibitors. LV diastolic function (impaired in 13 patients at the basal evaluation) improved in all subjects after treatment, with normalization in 10. The cold pressor test induced significant increases in blood pressure and heart rate. LV functional parameters remained unchanged both before and after treatment. Regression of myocardial hypertrophy induced by angiotensin-converting enzyme inhibitors does not impair the ability of the left ventricle to face acute increases of afterload. The improvement in diastolic function persists during the cold pressor test, which confirms that it is primarily due to regression of hypertrophy and is not simply a consequence of decrease in afterload induced by treatment.

VALVULAR HEART DISEASE

1442

Preoperative Diagnosis of Coronary Artery Disease in Patients with Valvular Heart Disease Using Technetium-99m Isonitrile Tomographic Imaging Together with High-Dose Dipyridamole and Handgrip Exercise

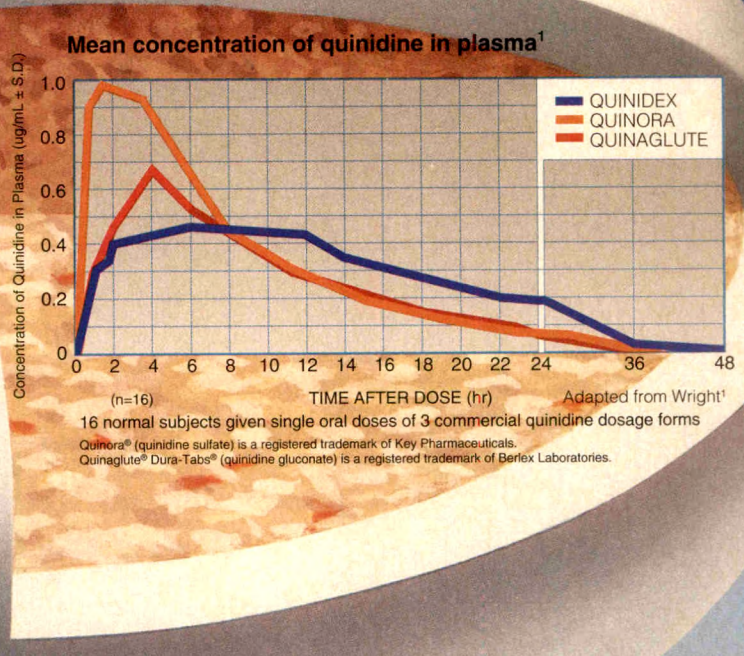
Raimo Kettunen, Heikki V. Huikuri, Juhani Heikkilä, and Juha T. Takkunen

Forty-seven patients with valvular heart disease were examined preoperatively with technetium-99m isonitrile tomography together with dipyridamole infusion (0.7 mg/kg) and handgrip exercise. Tomography correctly identified 18 of 21 patients with angiographically proven coronary artery disease (sensitivity 86%), but suggested 5 false positives among 26 normal cases (specificity 81%). Overall vessel sensitivity was 63%, and specificity was 92%. The frequency of side effects linked to dipyridamole was only 7%. No patient without angina pectoris and with a simultaneously negative finding by isotope tomography had a positive finding by coronary angiography.

Continued on page A37

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See brief summary of prescribing information on adjacent page.

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Trust experience.

The following is a brief summary only. Before prescribing, see complete prescribing information in Quinidex product labeling.

Contraindications: Intraventricular conduction defects. Complete A-V block. A-V conduction disorders caused by digitalis intoxication. Aberrant impulses and abnormal rhythms due to escape mechanisms. Idiosyncracy or hypersensitivity to quinidine or related cinchona derivatives. Myasthenia gravis.

Warnings: In the treatment of atrial flutter, reversion to sinus rhythm may be preceded by a progressive reduction in the degree of A-V block to a 1:1 ratio, resulting in an extremely rapid ventricular rate. This possible hazard may be reduced by digitalization prior to administration of quinidine.

Reports in the literature indicate that serum concentrations of digoxin may increase and may even double when quinidine is administered concurrently. Patients on concomitant therapy should be carefully monitored for digitalis toxicity. Reduction of digoxin dosage may have to be considered.

Manifestations of quinidine cardiotoxicity such as excessive prolongation of the QT interval, widening of the QRS complex and ventricular tachyarrhythmias mandate immediate discontinuation of the drug and/or close clinical and electrocardiographic monitoring.

In susceptible individuals, such as those with marginally compensated cardiovascular disease, quinidine may produce clinically important depression of cardiac function manifested by hypotension, bradycardia, or heartblock. Quinidine therapy should be carefully monitored in such individuals.

Quinidine should be used with extreme caution in patients with incomplete AV block since complete AV block and asystole may be produced. Quinidine may cause abnormalities of cardiac rhythm in digitalized patients and therefore should be used with caution in the presence of digitalis intoxication.

Quinidine should be used with caution in patients exhibiting renal, cardiac or hepatic insufficiency because of potential accumulation of quinidine in serum, leading to toxicity.

Patients taking quinidine occasionally have syncopal episodes which usually result from ventricular tachycardia or fibrillation. This syndrome has not been shown to be related to dose or serum levels. Syncopal episodes frequently terminate spontaneously or in response to treatment, but sometimes are fatal.

Cases of hepatotoxicity, including granulomatous hepatitis, due to quinidine hypersensitivity have been reported. Unexplained fever and/or elevation of hepatic enzymes, particularly in the early stages of therapy, warrant consideration of possible hepatotoxicity. Monitoring liver function during the first 4-8 weeks should be considered. Cessation of quinidine in these cases usually results in the disappearance of toxicity.

Precautions: *General*–All the precautions applying to regular quinidine therapy apply to this product. Hypersensitivity or anaphylactoid reactions to quinidine, although rare, should be considered, especially during the first weeks of therapy. Hospitalization for close clinical observation, electrocardiographic monitoring, and determination of serum quinidine levels are indicated when large doses of quinidine are used or with patients who present an increased risk.

Information for Patients–As with all solid dosage medications, Quinidex Extentabs should be taken with an adequate amount of fluid, preferably with the patient in an upright position to facilitate swallowing. They should be swallowed whole in order to preserve the controlled-release mechanism.

Laboratory Tests–Periodic blood counts and liver and kidney function tests should be performed during long-term therapy; the drug should be discontinued if blood dyscrasias or evidence of hepatic or renal dysfunction occurs.

Drug Interactions

Drug	Effect
Quinidine with anticholinergic drugs	Additive vagolytic effect
Quinidine with cholinergic drugs	Antagonism of cholinergic effects
Quinidine with carbonic anhydrase inhibitors, sodium bicarbonate, thiazide diuretics	Alkalinization of urine resulting in decreased excretion of quinidine
Quinidine with coumarin anticoagulants	Reduction of clotting factor concentrations
Quinidine with tubocurare, succinylcholine and decamethonium	Potentiation of neuromuscular blockade
Quinidine with phenothiazines and reserpine	Additive cardiac depressive effects
Quinidine with hepatic enzyme-inducing drugs (phenobarbital, phenytoin, rifampin)	Decreased plasma half-life of quinidine
Quinidine with digoxin	Increased serum concentration of digoxin (See Warnings)
Quinidine with amiodarone	Increased serum concentration of quinidine
Quinidine with cimetidine	Prolonged quinidine half-life and an increase in serum quinidine level
Quinidine with ranitidine	Premature ventricular contractions and/or bigeminy
Quinidine with verapamil	Increased quinidine half-life and an increase in serum quinidine level; potential hypotensive reactions
Quinidine with nifedipine	Decreased serum concentrations of quinidine

Carcinogenesis: Studies in animals have not been performed to evaluate the carcinogenic potential of quinidine.

Pregnancy, Teratogenic Effects: Pregnancy Category C. Animal reproduction studies have not been conducted with quinidine. There are no adequate and well-controlled studies in pregnant women. Quinidex Extentabs should be administered to a pregnant woman only if clearly indicated.

Nonteratogenic Effects: Like quinine, quinidine has been reported to have oxytocic properties. The significance of this property in the clinical setting has not been established.

Labor and Delivery–There is no known use for Quinidex Extentabs in labor and delivery. However, quinidine has been reported to have oxytocic properties. The significance of this property in the clinical setting has not been established.

Nursing Mothers–Because of passage of the drug into breast milk, caution should be exercised when Quinidex Extentabs are administered to a nursing woman.

Pediatric Use–There are no adequate and well-controlled studies establishing the safety and effectiveness of Quinidex Extentabs in children.

Adverse Reactions: Symptoms of cinchonism, such as ringing in the ears, loss of hearing, dizziness, lightheadedness, headache, nausea, and/or disturbed vision may appear in sensitive patients after a single dose of the drug. The most frequently encountered side effects to quinidine are gastrointestinal.

Gastrointestinal–Nausea, vomiting, abdominal pain, diarrhea, anorexia, granulomatous hepatitis (which may be preceded by fever), esophagitis.

Cardiovascular–Ventricular extrasystoles occurring at a rate of one or more every 6 normal beats; widening of the QRS complex and prolonged QT interval; complete A-V block; ventricular tachycardia and fibrillation; ventricular flutter; torsade de pointes; arterial embolism; hypotension; syncope.

Central Nervous System–Headache, vertigo, apprehension, excitement, confusion, delirium, dementia, ataxia, depression.

Ophthalmologic and Otologic–Disturbed hearing (tinnitus, decreased auditory acuity), disturbed vision (mydriasis, blurred vision, disturbed color perception, photophobia, diplopia, night blindness, scotomata), optic neuritis, reduced visual field.

Dermatologic–Cutaneous flushing with intense pruritus, photosensitivity, urticaria, rash, eczema, exfoliative eruptions, psoriasis, abnormalities of pigmentation.

Hypersensitivity–Angioedema, acute asthmatic episode, vascular collapse, respiratory arrest, hepatotoxicity, granulomatous hepatitis (See Warnings), purpura, vasculitis.

Hematologic–Thrombocytopenia, thrombocytopenic purpura, agranulocytosis, acute hemolytic anemia, hypoprothrombinemia, leukocytosis, shift to left in WBC differential neutropenia.

Immunologic–Systemic lupus erythematosus, lupus nephritis.

Miscellaneous–Fever, increase in serum skeletal muscle creatine phosphokinase, arthralgia, myalgia.

Rev. October 1987

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1. Wright GJ. Relative bioavailability and dosage form performance from single doses of quinidine as Quinidex Extentabs®, Quinaglute® Dura-Tabs®, and Quinora® in healthy male volunteers. Data on file, A.H. Robins Co., 1981.
2. Morganroth J, Hunter H. Comparative efficacy and safety of short-acting and sustained release quinidine in the treatment of patients with ventricular arrhythmias. *Am Heart J.* 1985;110:1176-1181.
3. IMS National Prescription Audit, May 1991.

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CARDIOMYOPATHY

1446
Frequency of Magnetic Resonance Signal Abnormalities of the Brain in Patients Aged <50 Years with Idiopathic Dilated Cardiomyopathy

Johann Dusleag, Werner Klein, Bernd Eber, Robert Gasser, Helmut Brussee, Brigitte Rotman, and Manfred Grisold

The purpose of the present study was to assess the prevalence of parenchymal abnormalities of the brain in young, neurologically asymptomatic patients with idiopathic dilated cardiomyopathy using magnetic resonance imaging. A higher frequency of ventricular enlargement ($p < 0.02$), cortical atrophy ($p < 0.01$) and white matter lesions ($p < 0.05$) was observed in patients than in healthy subjects. Cerebral infarcts were found in 4 patients ($p < 0.05$) who showed clinically severe limitation of functional capacity (New York Heart Association class III or IV). The data indicate a high incidence of parenchymal abnormalities of the brain in young patients with idiopathic dilated cardiomyopathy not suspected by clinical examination.

1451
Ventricular Arrhythmias in Dilated Cardiomyopathy as an Independent Prognostic Hallmark

Renata De Maria, Antonello Gavazzi, Angelo Caroli, Renato Ometto, Andrea Biagini, and Fulvio Camerini, on behalf of the Italian Multicenter Cardiomyopathy Study (SPIC) Group

Ventricular arrhythmias (VA) on Holter monitoring were evaluated in 218 patients with invasively documented idiopathic dilated cardiomyopathy to clarify their relation to pump dysfunction, and their prognostic role. Nonrepetitive forms of VA were present in 88 patients (group 1; 41%), ventricular pairs in 63 (group 2; 32%), and ventricular tachycardia in 67 (group 3; 27%). Only echocardiographic right ventricular dimensions ($p < 0.05$) and prevalence of VA during effort ($p = 0.0005$) differed significantly between groups. Arrhythmic variables were not correlated to pump function indexes. During a mean follow-up of 29 ± 16 months, 27 patients died from cardiac events, and 16 received transplants. Three-year survival probability was lower in groups 2 (0.82) and 3 (0.81) than in group 1 (0.94). By Cox multivariate analysis, VA severity ($p < 0.01$) was a major independent predictor of prognosis.

1458
Prevalence and Etiology of Idiopathic Dilated Cardiomyopathy (Summary of a National Heart, Lung, and Blood Institute Workshop)

Teri A. Manolio, Kenneth L. Baughman, Richard Rodeheffer, Thomas A. Pearson, J. David Bristow, Virginia V. Michels, Walter H. Abelmann, and William R. Harlan

Idiopathic dilated cardiomyopathy (IDC) is the primary indication for cardiac transplantation, with associated costs of approximately $177 mil-

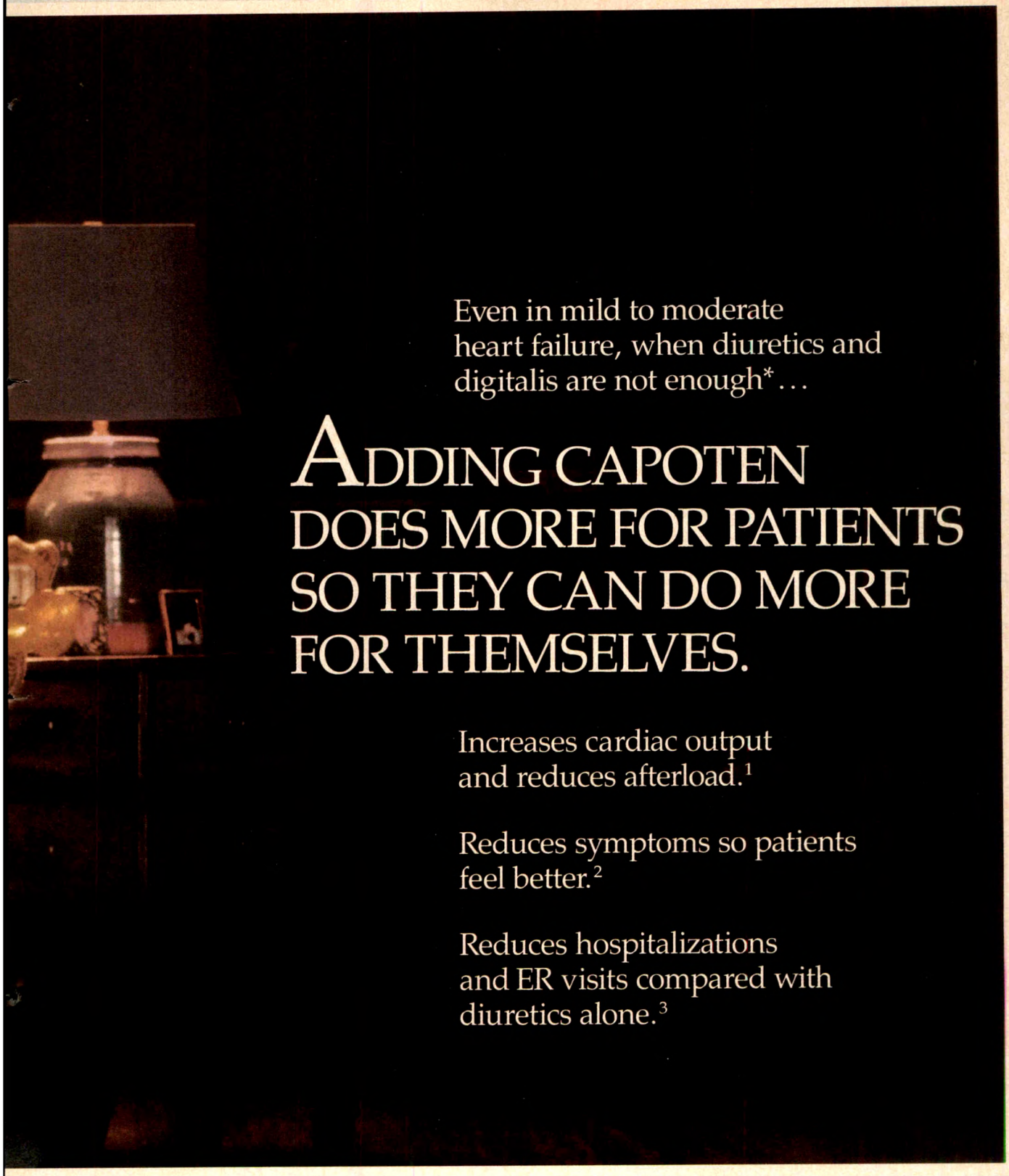
Continued on page A41



CAPOTEN is contraindicated in patients who are hypersensitive to this product. Angioedema has been reported in patients receiving ACE inhibitors.

***CAPOTEN should generally be added to diuretics and digitalis except when digitalis use is poorly tolerated or otherwise not feasible; add CAPOTEN when patients have not responded adequately.**

Please see brief summary, including the **boxed WARNING regarding Use in Pregnancy,** on the last page of this ad.



Even in mild to moderate heart failure, when diuretics and digitalis are not enough*...

ADDING CAPOTEN DOES MORE FOR PATIENTS SO THEY CAN DO MORE FOR THEMSELVES.

Increases cardiac output and reduces afterload.[1]

Reduces symptoms so patients feel better.[2]

Reduces hospitalizations and ER visits compared with diuretics alone.[3]

IN HEART FAILURE

CAPOTEN®
(captopril)

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CAPOTEN® TABLETS
Captopril Tablets

USE IN PREGNANCY

When used in pregnancy during the second and third trimesters, ACE inhibitors can cause injury and even death to the developing fetus. When pregnancy is detected, CAPOTEN should be discontinued as soon as possible. **See WARNINGS: Fetal/Neonatal Morbidity and Mortality.**

CONTRAINDICATIONS: CAPOTEN is contraindicated in patients who are hypersensitive to this product or any other angiotensin-converting enzyme inhibitor (e.g., a patient who has experienced angioedema during therapy with any other ACE inhibitor).

WARNINGS: Angioedema: Angioedema involving the extremities, face, lips, mucous membranes, tongue, glottis or larynx has been seen in patients treated with ACE inhibitors, including captopril. If angioedema involves the tongue, glottis or larynx, airway obstruction may occur and be fatal. Emergency therapy, including but not necessarily limited to, subcutaneous administration of a 1:1000 solution of epinephrine should be promptly instituted.

Neutropenia / Agranulocytosis: Neutropenia (< 1000/mm³) with myeloid hypoplasia has resulted from use of captopril. About half of the neutropenic patients developed systemic or oral cavity infections or other features of the syndrome of agranulocytosis. The risk of neutropenia is dependent on the clinical status of the patient:

In clinical trials in patients with hypertension who have normal renal function (serum creatinine less than 1.6 mg/dL and no collagen vascular disease), neutropenia has been seen in one patient out of over 8,600 exposed. In patients with some degree of renal failure (serum creatinine at least 1.6 mg/dL) but no collagen vascular disease, the risk in clinical trials was about 1 per 500. Doses were relatively high in these patients, particularly in view of their diminished renal function. In patients with collagen vascular diseases (e.g., systemic lupus erythematosus, scleroderma) and impaired renal function, neutropenia occurred in 3.7% of patients in clinical trials. While none of the over 750 patients in formal clinical trials of heart failure developed neutropenia, it has occurred during the subsequent clinical experience. Of reported cases, about half had serum creatinine ≥ 1.6 mg/dL and more than 75% received procainamide. In heart failure, it appears that the same risk factors for neutropenia are present.

Neutropenia has appeared usually within 3 months after starting therapy, associated with myeloid hypoplasia and frequently accompanied by erythroid hypoplasia and decreased numbers of megakaryocytes (e.g., hypoplastic bone marrow and pancytopenia); anemia and thrombocytopenia were sometimes seen. Neutrophils generally returned to normal in about 2 weeks after captopril was discontinued, and serious infections were limited to clinically complex patients. About 13% of the cases of neutropenia have ended fatally, but almost all fatalities were in patients with serious illness, having collagen vascular disease, renal failure, heart failure or immunosuppressant therapy, or a combination of these complicating factors. **Evaluation of the hypertensive or heart failure patient should always include assessment of renal function.** If captopril is used in patients with impaired renal function, white blood cell and differential counts should be evaluated prior to starting treatment and at approximately 2-week intervals for about 3 months, then periodically. In patients with collagen vascular disease or who are exposed to other drugs known to affect the white cells or immune response, particularly when there is impaired renal function, captopril should be used only after an assessment of benefit and risk, and then with caution. All patients treated with captopril should be told to report any signs of infection (e.g., sore throat, fever). If infection is suspected, perform white cell counts without delay. Since discontinuation of captopril and other drugs has generally led to prompt return of the white count to normal, upon confirmation of neutropenia (neutrophil count < 1000/mm³) withdraw captopril and closely follow the patient's course.

Proteinuria: Total urinary proteins >1 g per day were seen in about 0.7% of patients on captopril. About 90% of affected patients had evidence of prior renal disease or received high doses (>150 mg/day), or both. The nephrotic syndrome occurred in about one-fifth of proteinuric patients. In most cases, proteinuria subsided or cleared within 6 months whether or not captopril was continued. The BUN and creatinine were seldom altered in proteinuric patients. Since most cases of proteinuria occurred by the 8th month of therapy with captopril, patients with prior renal disease or those receiving captopril at doses >150 mg per day, should have urinary protein estimates (dip-stick on 1st morning urine) before therapy, and periodically thereafter.

Hypotension: Excessive hypotension was rarely seen in hypertensive patients but is a possible consequence of captopril use in salt/volume depleted persons (such as those treated vigorously with diuretics), patients with heart failure or those patients undergoing renal dialysis. (See PRECAUTIONS: Drug Interactions.) In heart failure, where the blood pressure was either normal or low, transient decreases in mean blood pressure >20% were recorded in about half of the patients. This transient hypotension is more likely to occur after any of the first several doses and is usually well tolerated, although rarely it has been associated with arrhythmia or conduction defects. A starting dose of 6.25 or 12.5 mg tid may minimize the hypotensive effect. Patients should be followed closely for the first 2 weeks of treatment and whenever the dose of captopril and/or diuretic is increased.

BECAUSE OF THE POTENTIAL FALL IN BLOOD PRESSURE IN THESE PATIENTS, THERAPY SHOULD BE STARTED UNDER VERY CLOSE MEDICAL SUPERVISION.

Fetal / Neonatal Morbidity and Mortality: ACE inhibitors can cause fetal and neonatal morbidity and death when administered to pregnant women. Several dozen cases have been reported in the world literature. When pregnancy is detected, ACE inhibitors should be discontinued as soon as possible.

The use of ACE inhibitors during the second and third trimesters of pregnancy has been associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death. Oligohydramnios has also been reported, presumably resulting from decreased fetal renal function; oligohydramnios in this setting has been associated with fetal limb contractures, craniofacial deformation, and hypoplastic lung development. Prematurity, intrauterine growth retardation, and patent ductus arteriosus have also been reported, although it is not clear whether these occurrences were due to the ACE-inhibitor exposure.

These adverse effects do not appear to have resulted from intrauterine ACE-inhibitor exposure that has been limited to the first trimester. Mothers whose embryos and fetuses are exposed to ACE inhibitors only during the first trimester should be so informed. Nonetheless, when patients become pregnant, physicians should make every effort to discontinue the use of captopril as soon as possible.

Rarely (probably less often than once in every thousand pregnancies), no alternative to ACE inhibitors will be found. In these rare cases, the mothers should be apprised of the potential hazards to their fetuses, and serial ultrasound examinations should be performed to assess the intraamniotic environment.

If oligohydramnios is observed, captopril should be discontinued unless it is considered life-saving for the mother. Contraction stress testing (CST), a non-stress test (NST), or biophysical profiling (BPP) may be appropriate, depending upon the week of pregnancy. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury.

Infants with histories of *in utero* exposure to ACE inhibitors should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion. Exchange transfusion or dialysis may be required as a means of reversing hypotension and/or substituting for disordered renal function. While captopril may be removed from the adult circulation by hemodialysis, there is inadequate data concerning the effectiveness of hemodialysis for removing it from the circulation of neonates or children. Peritoneal dialysis is not effective for removing captopril; there is no information concerning exchange transfusion for removing captopril from the general circulation.

When captopril was given to rabbits at doses about 0.8 to 70 times (on a mg/kg basis) the maximum recommended human dose, low incidences of craniofacial malformations were seen. No teratogenic effects of captopril were seen in studies of pregnant rats and hamsters. On a mg/kg basis, the doses used were up to 150 times (in hamsters) and 625 times (in rats) the maximum recommended human dose.

PRECAUTIONS: General: *Impaired Renal Function*—Hypertension–Some hypertensive patients with renal disease, particularly those with severe renal artery stenosis, have developed increases in BUN and serum creatinine. It may be necessary to reduce captopril dosage and/or discontinue diuretic. For some of these patients, normalization of blood pressure and maintenance of adequate renal perfusion may not be possible. Heart Failure—About 20% of patients develop stable elevations of BUN and serum creatinine >20% above normal or baseline upon long-term treatment. Less than 5% of patients, generally with severe preexisting renal disease, required discontinuation due to progressively increasing creatinine. (See DOSAGE AND ADMINISTRATION, ADVERSE REACTIONS: Altered Laboratory Findings.) *Hyperkalemia:* Elevations in serum potassium have been observed in some patients treated with ACE inhibitors, including captopril. When treated with ACE inhibitors, patients at risk for the development of hyperkalemia include those with: renal insufficiency; diabetes mellitus; and those using concomitant potassium-sparing diuretics, potassium supplements or potassium-containing salt substitutes; or other drugs associated with increases in serum potassium. (See PRECAUTIONS: Drug Interactions; ADVERSE REACTIONS: Altered Laboratory Findings.) *Cough*—Cough has been reported with the use of ACE inhibitors. Characteristically, the cough is nonproductive, persistent and resolves after discontinuation of therapy. ACE inhibitor-induced cough should be considered as part of the differential diagnosis of cough. *Valvular Stenosis*—A theoretical concern, for risk of decreased coronary perfusion, has been noted regarding vasodilator treatment in patients with aortic stenosis due to decreased afterload reduction. *Surgery/Anesthesia*—If hypotension occurs during surgery or anesthesia, and is considered due to the effects of captopril, it is correctable by volume expansion.

Pregnancy. Female patients of childbearing age should be told about the consequences of second- and third-trimester exposure to ACE inhibitors, and they should also be told that these consequences do not appear to have resulted from intrauterine ACE-inhibitor exposure that has been limited to the first trimester. These patients should be asked to report pregnancies to their physicians as soon as possible.

Drug Interactions: *Hypotension–Patients on Diuretic Therapy*—Precipitous reduction of blood pressure may occasionally occur within the 1st hour after administration of the initial captopril dose in patients on diuretics, especially those recently placed on diuretics, and those on severe dietary salt restriction or dialysis. This possibility can be minimized by either discontinuing the diuretic or increasing the salt intake about 1 week prior to initiation of captopril therapy or by initiating therapy with small doses (6.25 or 12.5 mg). Alternatively, provide medical supervision for at least 1 hour after the initial dose.

Agents Having Vasodilator Activity—In heart failure patients, vasodilators should be administered with caution.

Agents Causing Renin Release—Captopril's effect will be augmented by antihypertensive agents that cause renin release.

Agents Affecting Sympathetic Activity—The sympathetic nervous system may be especially important in supporting blood pressure in patients receiving captopril alone or with diuretics. Beta-adrenergic blocking drugs add some further antihypertensive effect to captopril, but the overall response is less than additive. Therefore, use agents affecting sympathetic activity (e.g., ganglionic blocking agents or adrenergic neuron blocking agents) with caution.

Agents Increasing Serum Potassium—Give potassium-sparing diuretics or potassium supplements only for documented hypokalemia, and then with caution, since they may lead to a significant increase of serum potassium. Use potassium-containing salt substitutes with caution.

Inhibitors of Endogenous Prostaglandin Synthesis—Indomethacin and other nonsteroidal anti-inflammatory agents may reduce the antihypertensive effect of captopril, especially in low renin hypertension.

Lithium—Increased serum lithium levels and symptoms of lithium toxicity have been reported in patients receiving concomitant lithium and ACE inhibitor therapy. These drugs should be coadministered with caution and frequent monitoring of serum lithium levels is recommended. If a diuretic is also used, it may increase the risk of lithium toxicity.

Drug/Laboratory Test Interaction: Captopril may cause a false-positive urine test for acetone.

Carcinogenesis, Mutagenesis and Impairment of Fertility: Two-year studies with doses of 50 to 1350 mg/kg/day in mice and rats failed to show any evidence of carcinogenic potential. Studies in rats have revealed no impairment of fertility.

Pregnancy Categories C (first trimester) and D (second and third trimesters)
See WARNINGS: Fetal/Neonatal Morbidity and Mortality.

Nursing Mothers: Concentrations of captopril in human milk are approximately one percent of those in maternal blood. Because of the potential for serious adverse reactions in nursing infants from captopril, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of CAPOTEN to the mother. (See PRECAUTIONS: Pediatric Use.)

Pediatric Use: Safety and effectiveness in children have not been established. There is limited experience reported in the literature with the use of captopril in the pediatric population; dosage, on a weight basis, was generally reported to be comparable to or less than that used in adults.

Infants, especially newborns, may be more susceptible to the adverse hemodynamic effects of captopril. Excessive, prolonged and unpredictable decreases in blood pressure and associated complications, including oliguria and seizures, have been reported.

CAPOTEN (captopril) should be used in children only if other measures for controlling blood pressure have not been effective.

ADVERSE REACTIONS: Reported incidences are based on clinical trials involving approximately 7000 patients.

Renal: About 1 of 100 patients developed proteinuria (see WARNINGS). Renal insufficiency, renal failure, nephrotic syndrome, polyuria, oliguria, and urinary frequency in 1 to 2 of 1000 patients.

Hematologic: Neutropenia/agranulocytosis has occurred (see WARNINGS). Anemia, thrombocytopenia, and pancytopenia have been reported.

Dermatologic: Rash, (usually maculopapular, rarely urticarial), often with pruritus, and sometimes with fever and eosinophilia, in about 4 to 7 of 100 patients (depending on renal status and dose), usually during the 1st 4 weeks of therapy. Pruritus, without rash, in about 2 of 100 patients. A reversible associated pemphigoid-like lesion, and photosensitivity, have also been reported. Flushing or pallor in 2 to 5 of 1000 patients.

Cardiovascular: Hypotension may occur; see WARNINGS and PRECAUTIONS [Drug Interactions] for discussion of hypotension with captopril therapy. Tachycardia, chest pain, and palpitations each in about 1 of 100 patients. Angina pectoris, myocardial infarction, Raynaud's syndrome, and congestive heart failure each in 2 to 3 of 1000 patients.

Dysgeusia: Approximately 2 to 4 (depending on renal status and dose) of 100 patients developed a diminution or loss of taste perception; taste impairment is reversible and usually self-limited even with continued drug use (2 to 3 months).

Angioedema: Angioedema involving the extremities, face, lips, mucous membranes, tongue, glottis or larynx has been reported in approximately one in 1000 patients. Angioedema involving the upper airways has caused fatal airway obstruction. (See WARNINGS.)

Cough: Cough has been reported in 0.5-2% of patients treated with captopril in clinical trials (see PRECAUTIONS: General: *Cough*).

The following have been reported in about 0.5 to 2 percent of patients but did not appear at increased frequency compared to placebo or other treatments used in controlled trials: gastric irritation, abdominal pain, nausea, vomiting, diarrhea, anorexia, constipation, aphthous ulcers, peptic ulcer, dizziness, headache, malaise, fatigue, insomnia, dry mouth, dyspnea, cough, alopecia, paresthesias.

Other clinical adverse effects reported since the drug was marketed are listed below by body system. In this setting, an incidence or causal relationship cannot be accurately determined.

General: Asthenia, gynecomastia.
Cardiovascular: Cardiac arrest, cerebrovascular accident/insufficiency, rhythm disturbances, orthostatic hypotension, syncope.
Dermatologic: Bullous pemphigus, erythema multiforme (including Stevens-Johnson syndrome), exfoliative dermatitis.
Gastrointestinal: Pancreatitis, glossitis, dyspepsia.
Hematologic: Anemia, including aplastic and hemolytic.
Hepatobiliary: Jaundice, hepatitis, including rare cases of necrosis, cholestasis.
Metabolic: Symptomatic hyponatremia.
Musculoskeletal: Myalgia, myasthenia.
Nervous/Psychiatric: Ataxia, confusion, depression, nervousness, somnolence.
Respiratory: Bronchospasm, eosinophilic pneumonitis, rhinitis.
Special Senses: Blurred vision.
Urogenital: Impotence.

As with other ACE inhibitors, a syndrome has been reported which may include: fever, myalgia, arthralgia, interstitial nephritis, vasculitis, rash or other dermatologic manifestations, eosinophilia and an elevated ESR.

Fetal/Neonatal Morbidity and Mortality
See WARNINGS: Fetal/Neonatal Morbidity and Mortality.

Altered Laboratory Findings: *Serum Electrolytes:* Hyperkalemia: small increases in serum potassium, especially in patients with renal impairment (see PRECAUTIONS).

Hyponatremia: particularly in patients receiving a low sodium diet or concomitant diuretics.

BUN/Serum Creatinine: Transient elevations of BUN or serum creatinine especially in volume or salt depleted patients or those with renovascular hypertension may occur. Rapid reduction of long-standing or markedly elevated blood pressure can result in decreases in the glomerular filtration rate and, in turn, lead to increases in BUN or serum creatinine.

Hematologic: A positive ANA has been reported.

Liver Function Tests: Elevations of liver transaminases, alkaline phosphatase, and serum bilirubin have occurred.

OVERDOSAGE: Primary concern is correction of hypotension. Volume expansion with an I.V. infusion of normal saline is the treatment of choice for restoration of blood pressure.

While captopril may be removed from the adult circulation by hemodialysis, there is inadequate data concerning the effectiveness of hemodialysis for removing it from the circulation of neonates or children. Peritoneal dialysis is not effective for removing captopril; there is no information concerning exchange transfusion for removing captopril from the general circulation.

DOSAGE AND ADMINISTRATION: CAPOTEN (captopril) should be taken one hour before meals. In hypertension, CAPOTEN may be dosed bid or tid. Dosage must be individualized; see DOSAGE AND ADMINISTRATION section of package insert for detailed information regarding dosage in hypertension and in heart failure. Because CAPOTEN (captopril) is excreted primarily by the kidneys, dosage adjustments are recommended for patients with impaired renal function.

Consult package insert before prescribing CAPOTEN (captopril).

HOW SUPPLIED: Available in tablets of: 12.5 mg in bottles of 100 and 1000; 25 mg in bottles of 100 and 1000; 50 mg in bottles of 100 and 1000; 100 mg of bottles of 100; and in UNIMATIC® unit-dose packs of 100 tablets. (J3-658Z)

References: 1. Physicians' Desk Reference®, 45th ed, Oradell, NJ. Medical Economics Co Inc, 1991, pp 2141-2143. **2.** Captopril Multicenter Research Group: A placebo-controlled trial of captopril in refractory chronic congestive heart failure. *JACC* 2:755-763, 1983. **3.** The Captopril-Digoxin Multicenter Research Group: Comparative effects of therapy with captopril and digoxin in patients with mild to moderate heart failure. *JAMA* 259:539-544, 1988.

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0522-517

Issued: May 1992

lion per year. Recognizing the economic implications of IDC, the increasing incidence, and the limited information on pathogenesis and prognosis, the National Heart, Lung, and Blood Institute convened a workshop on the Prevalence and Etiology of Idiopathic Dilated Cardiomyopathy on June 13 to 14, 1991. Standardized diagnostic criteria for use in observational and interventional trials were developed, and priorities for future research were proposed. Population-based registries and nested case-control studies, where feasible, are appropriate study designs for tracking incidence and prevalence, and for identifying risk factors, respectively. Interventional studies should focus on secondary prevention, through modifying immune-mediated damage in clinically evident dilated cardiomyopathy, and through prevention of sudden death in patients with the disorder. Primary prevention trials must await the identification of modifiable risk factors and of appropriate and effective interventions.

CONGENITAL HEART DISEASE

1467

Clinical Impact of Balloon Angioplasty for Branch Pulmonary Arterial Stenosis

Martin C. K. Hosking, Constantin Thomaidis, Robert Hamilton, Patricia E. Burrows, Robert M. Freedom, and Lee N. Benson

The clinical impact of percutaneous balloon angioplasty on the future management of patients with native or postoperative pulmonary arterial stenosis was reviewed. Seventy-four patients underwent 110 angioplasty procedures. Pulmonary artery dilatation was acutely successful in 53% of patients, with recurrent stenosis in 17%, and complications in 5%. Future management was favorably influenced in only 35% (26 of 74) of patients by the dilatation procedure. No patient previously considered inoperable was subsequently considered suitable for surgical repair. No correlations were found between success and cardiac diagnosis ($p = 0.48$), site of stenosis ($p = 0.78$), balloon-vessel ratio ($p = 0.42$), or whether the stenosis consisted of native or synthetic material ($p = 0.22$). Although the effect of dilatation appears transient, it remains prudent to offer angioplasty as a therapeutic modality. Future integration of implantable intravascular stent devices may prove to be efficacious for many of these patients.

1471

Outcome of Prenatally Detected Cardiac Malformations

John F. Smythe, Joshua A. Copel, and Charles S. Kleinman

The impact of prenatal detection of congenital heart disease by fetal echocardiography on outcome (pre- and postnatal) of 170 cardiac defects diagnosed in utero is documented. Of 170 cases, 55 (32%) had major extracardiac malformations and 45 (28%) had chromosomal abnormalities (16 had both). Elective termination was chosen in 77 pregnancies. Of 93 continuing pregnancies 15 were stillborn and 43 died postnatally (48% of these fetuses and infants had extracardiac or chromosomal anomalies, or both). Thirty-five patients survive at 1 to 80 months (mean 36); aneuploidy or extracardiac defects are present in 20% of survivors. Nonimmune hydrops was fatal. Clearly, the prognosis of prenatally diagnosed

cardiac lesions is negatively influenced by the presence of cardiac failure, aneuploidy or extracardiac malformations, or a combination. Optimal counseling and management requires the identification of these conditions when present.

MISCELLANEOUS

1475
Cardiac Characteristics and Postoperative Courses in Cushing's Syndrome
Norihiko Sugihara, Masami Shimizu, Yoshihito Kita, Kuniyoshi Shimizu, Hidekazu Ino, Isamu Miyamori, Hajime Nakabayashi, and Ryoyu Takeda

To assess the cardiac characteristics and postoperative courses in Cushing's syndrome, electrocardiograms and echocardiograms were recorded to study 12 consecutive patients and compared with those of essential hypertension and primary aldosteronism. Before adrenalectomy, common electrocardiographic abnormalities consisted of high-voltage QRS complexes and negative T waves. Echocardiograms showed left ventricular hypertrophy in 9 patients and all patients had evidence of asymmetric septal hypertrophy. Interventricular septum in Cushing's syndrome was extremely thicker and the frequency of asymmetric septal hypertrophy was extremely higher than that of essential hypertension and primary aldosteronism. Abnormal electrocardiographic findings had normalized, the thickness of interventricular septum had decreased and asymmetric septal hypertrophy had disappeared after operation. From these results it is thought that not only high aortic pressure but also excessive plasma cortisol may be etiologic factors in the progression of left ventricular hypertrophy in Cushing's syndrome.

BRIEF REPORTS

1481
Effect of Balloon Material on Coronary Angioplasty
Michael R. Mooney, Jodi Fishman Mooney, Terrence F. Longe, and Robert O. Brandenburg, Jr.

1483
Extent and Severity of Abnormal Left Ventricular Wall Motion Detected by Exercise Echocardiography During Painful and Silent Ischemia
Thomas H. Marwick, James J. Nemec, Julius Torelli, Ernesto E. Salcedo, and William J. Stewart

1484
Clinical Significance of Abrupt Vasodepression During Dobutamine Stress Echocardiography
Peter K. Mazeika, Aleksander Nadazdin, and Celia M. Oakley

Continued on page A45

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(FOR FULL PRESCRIBING INFORMATION, SEE PACKAGE INSERT.)

INDICATIONS AND USAGE: Hypertension: TENORMIN is indicated in the management of hypertension. It may be used alone or concomitantly with other antihypertensive agents, particularly with a thiazide-type diuretic.

Angina Pectoris Due to Coronary Atherosclerosis: TENORMIN is indicated for the long-term management of patients with angina pectoris.

Acute Myocardial Infarction: TENORMIN is indicated in the management of hemodynamically stable patients with definite or suspected acute myocardial infarction to reduce cardiovascular mortality. Treatment can be initiated as soon as the patient's clinical condition allows. (See DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS.) In general, there is no basis for treating patients like those who were excluded from the ISIS-1 trial (blood pressure less than 100 mm Hg systolic, heart rate less than 50 bpm) or have other reasons to avoid beta blockade. As noted above, some subgroups (eg, elderly patients with systolic blood pressure below 120 mm Hg) seemed less likely to benefit.

CONTRAINDICATIONS: TENORMIN is contraindicated in sinus bradycardia, heart block greater than first degree, cardiogenic shock, and overt cardiac failure. (See WARNINGS.)

WARNINGS: Cardiac Failure: Sympathetic stimulation is necessary in supporting circulatory function in congestive heart failure, and beta blockade carries the potential hazard of further depressing myocardial contractility and precipitating more severe failure. In patients who have congestive heart failure controlled by digitalis and/or diuretics, TENORMIN should be administered cautiously. Both digitalis and atenolol slow AV conduction.

In patients with acute myocardial infarction, cardiac failure which is not promptly and effectively controlled by 80 mg of intravenous furosemide or equivalent therapy is a contraindication to beta-blocker treatment.

In Patients Without a History of Cardiac Failure: Continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or be given a diuretic and the response observed closely. If cardiac failure continues despite adequate digitalization and diuresis, TENORMIN should be withdrawn. (See DOSAGE AND ADMINISTRATION.)

Cessation of Therapy with TENORMIN: Patients with coronary artery disease, who are being treated with TENORMIN, should be advised against abrupt discontinuation of therapy. Severe exacerbation of angina and the occurrence of myocardial infarction and ventricular arrhythmias have been reported in angina patients following the abrupt discontinuation of therapy with beta blockers. The last two complications may occur with or without preceding exacerbation of the angina pectoris. As with other beta blockers, when discontinuation of TENORMIN is planned, the patient should be carefully observed and advised to limit physical activity to a minimum. If the angina worsens or acute coronary insufficiency develops, it is recommended that TENORMIN be promptly reinstituted, at least temporarily. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue TENORMIN therapy abruptly even in patients treated only for hypertension. (See DOSAGE AND ADMINISTRATION.)

Bronchospastic Diseases: PATIENTS WITH BRONCHOSPASTIC DISEASE SHOULD, IN GENERAL, NOT RECEIVE BETA BLOCKERS. Because of its relative $beta_1$ selectivity, however, TENORMIN may be used with caution in patients with bronchospastic disease who do not respond to, or cannot tolerate, other antihypertensive treatment. Since $beta_1$ selectivity is not absolute, the lowest possible dose of TENORMIN should be used with therapy initiated at 50 mg and a $beta_2$-stimulating agent (bronchodilator) should be made available. If dosage must be increased, dividing the dose should be considered in order to achieve lower peak blood levels.

Anesthesia and Major Surgery: It is not advisable to withdraw beta-adrenoreceptor blocking drugs prior to surgery in the majority of patients. However, care should be taken when using anesthetic agents such as those which may depress the myocardium. Vagal dominance, if it occurs, may be corrected with atropine (1-2 mg IV).

Additionally, caution should be used when TENORMIN I.V. Injection is administered concomitantly with such agents.

TENORMIN, like other beta blockers, is a competitive inhibitor of beta-receptor agonists and its effects on the heart can be reversed by administration of such agents: eg, dobutamine or isoproterenol with caution (see section on OVERDOSAGE).

Diabetes and Hypoglycemia: TENORMIN should be used with caution in diabetic patients if a beta-blocking agent is required. Beta blockers may mask tachycardia occurring with hypoglycemia, but other manifestations such as dizziness and sweating may not be significantly affected. At recommended doses TENORMIN does not potentiate insulin-induced hypoglycemia and, unlike nonselective beta blockers, does not delay recovery of blood glucose to normal levels.

Thyrotoxicosis: Beta-adrenergic blockade may mask certain clinical signs (eg, tachycardia) of hyperthyroidism. Patients suspected of having thyroid disease should be monitored closely when administering TENORMIN I.V. Injection. Abrupt withdrawal of beta blockade might precipitate a thyroid storm; therefore, patients suspected of developing thyrotoxicosis from whom TENORMIN therapy is to be withdrawn should be monitored closely. (See DOSAGE AND ADMINISTRATION.)

PRECAUTIONS: General: Patients already on a beta blocker must be evaluated carefully before TENORMIN is administered. Initial and subsequent TENORMIN dosages can be adjusted downward depending on clinical observations including pulse and blood pressure.

Impaired Renal Function: The drug should be used with caution in patients with impaired renal function. (SEE DOSAGE AND ADMINISTRATION.)

Drug Interactions: Catecholamine-depleting drugs (eg, reserpine) may have an additive effect when given with beta-blocking agents. Patients treated with TENORMIN plus a catecholamine depletor should therefore be closely observed for evidence of hypotension and/or marked bradycardia which may produce vertigo, syncope, or postural hypotension.

Should it be decided to discontinue therapy in patients receiving beta blockers and clonidine concurrently, the beta blocker should be discontinued several days before the gradual withdrawal of clonidine.

Caution should be exercised with TENORMIN I.V. Injection when given in close proximity with drugs that may also have a depressant effect on myocardial contractility. On rare occasions, concomitant use of intravenous beta blockers and intravenous verapamil has resulted in serious adverse reactions, especially in patients with severe cardiomyopathy, congestive heart failure, or recent myocardial infarction.

Information on concurrent usage of atenolol and aspirin is limited. Data from several studies, ie, TIMI-II, ISIS-2, currently do not suggest any clinical interaction between aspirin and beta blockers in the acute myocardial infarction setting.

While taking beta blockers, patients with a history of anaphylactic reaction to a variety of allergens may have a more severe reaction on repeated challenge, either accidental, diagnostic, or therapeutic. Such patients may be unresponsive to the usual doses of epinephrine used to treat the allergic reaction.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Two long-term (maximum dosing duration of 18 or 24 months) rat studies and one long-term (maximum dosing duration of 18 months) mouse study, each employing dose levels as high as 300 mg/kg/day or 150 times the maximum recommended human antihypertensive dose,* did not indicate a carcinogenic potential of atenolol. A third (24 month) rat study, employing doses of 500 and 1,500 mg/kg/day (250 and 750 times the maximum recommended human antihypertensive dose*) resulted in increased incidences of benign adrenal medullary tumors in males and females, mammary fibroadenomas in females, and anterior pituitary adenomas and thyroid parafollicular cell carcinomas in males. No evidence of a mutagenic potential of atenolol was uncovered in the dominant lethal test (mouse), in vivo cytogenetics test (Chinese hamster) or Ames test *(S typhimurium)*.

Fertility of male or female rats (evaluated at dose levels as high as 200 mg/kg/day or 100 times the maximum recommended human dose*) was unaffected by atenolol administration.

Animal Toxicology: Chronic studies employing oral atenolol performed in animals have revealed the occurrence of vacuolation of epithelial cells of Brunner's glands in the duodenum of both male and female dogs at all tested dose levels of atenolol (starting at 15 mg/kg/day or 7.5 times the maximum recommended human antihypertensive dose*) and increased incidence of atrial degeneration of hearts of male rats at 300 but not 150 mg atenolol/kg/day (150 and 75 times the maximum recommended human antihypertensive dose,* respectively).

Usage in Pregnancy: Pregnancy Category C: Atenolol has been shown to produce a dose-related increase in embryo/fetal resorptions in rats at doses equal to or greater than 50 mg/kg/day or 25 or more times the maximum recommended human antihypertensive dose.* Although similar effects were not seen in rabbits, the compound was not evaluated in rabbits at doses above 25 mg/kg/day or 12.5 times the maximum recommended human antihypertensive dose.* There are no adequate and well-controlled studies in pregnant women. TENORMIN should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

*Based on the maximum dose of 100 mg/day in a 50 kg patient.

Nursing Mothers: Atenolol is excreted in human breast milk at a ratio of 1.5 to 6.8 when compared to the concentration in plasma. Caution should be exercised when TENORMIN is administered to a nursing woman. Clinically significant bradycardia has been reported in breast fed infants. Premature infants, or infants with impaired renal function, may be more likely to develop adverse effects.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: Most adverse effects have been mild and transient.

The frequency estimates in the following table were derived from controlled studies in hypertensive patients in which adverse reactions were either volunteered by the patient (US studies) or elicited, eg, by checklist (foreign studies). The reported frequency of elicited adverse effects was higher for both TENORMIN and placebo-treated patients than when these reactions were volunteered. Where frequency of adverse effects of TENORMIN and placebo is similar, causal relationship to TENORMIN is uncertain.

	Volunteered (US Studies)		Total - Volunteered and Elicited (Foreign + US Studies)	
	Atenolol (n = 164) %	Placebo (n = 206) %	Atenolol (n = 399) %	Placebo (n = 407) %
CARDIOVASCULAR				
Bradycardia	3	0	3	0
Cold Extremities	0	0.5	12	5
Postural Hypotension	2	1	4	5
Leg Pain	0	0.5	3	1
CENTRAL NERVOUS SYSTEM/ NEUROMUSCULAR				
Dizziness	4	1	13	6
Vertigo	2	0.5	2	0.2
Light-headedness	1	0	3	0.7
Tiredness	0.6	0.5	26	13
Fatigue	3	1	6	5
Lethargy	1	0	3	0.7
Drowsiness	0.6	0	2	0.5
Depression	0.6	0.5	12	9
Dreaming	0	0	3	1
GASTROINTESTINAL				
Diarrhea	2	0	3	2
Nausea	4	1	3	1
RESPIRATORY (see WARNINGS)				
Wheeziness	0	0	3	3
Dyspnea	0.6	1	6	4

Acute Myocardial Infarction: In a series of investigations in the treatment of acute myocardial infarction, bradycardia and hypotension occurred more commonly, as expected for any beta blocker, in atenolol-treated patients than in control patients. However, these usually responded to atropine and/or to withholding further dosage of atenolol. The incidence of heart failure was not increased by atenolol. Inotropic agents were infrequently used. The reported frequency of these and other events occurring during these investigations is given in the following table.

In a study of 477 patients, the following adverse events were reported during either intravenous and/or oral atenolol administration:

	Conventional Therapy Plus Atenolol (n=244)		Conventional Therapy Alone (n=233)	
Bradycardia	43	(18%)	24	(10%)
Hypotension	60	(25%)	34	(15%)
Bronchospasm	3	(1.2%)	2	(0.9%)
Heart Failure	46	(19%)	56	(24%)
Heart Block	11	(4.5%)	10	(4.3%)
BBB + Major Axis Deviation	16	(6.6%)	28	(12%)
Supraventricular Tachycardia	28	(11.5%)	45	(19%)
Atrial Fibrillation	12	(5%)	29	(11%)
Atrial Flutter	4	(1.6%)	7	(3%)
Ventricular Tachycardia	39	(16%)	52	(22%)
Cardiac Reinfarction	0	(0%)	6	(2.6%)
Total Cardiac Arrests	4	(1.6%)	16	(6.9%)
Nonfatal Cardiac Arrests	4	(1.6%)	12	(5.1%)
Deaths	7	(2.9%)	16	(6.9%)
Cardiogenic Shock	1	(0.4%)	4	(1.7%)
Development of Ventricular Septal Defect	0	(0%)	2	(0.9%)
Development of Mitral Regurgitation	0	(0%)	2	(0.9%)
Renal Failure	1	(0.4%)	0	(0%)
Pulmonary Emboli	3	(1.2%)	0	(0%)

In the subsequent International Study of Infarct Survival (ISIS-1) including over 16,000 patients of whom 8,037 were randomized to receive TENORMIN treatment, the dosage of intravenous and subsequent oral TENORMIN was either discontinued or reduced for the following reasons:

	Reasons for Reduced Dosage IV Atenolol Reduced Dose (< 5mg)*		Oral Partial Dose	
Hypotension/Bradycardia	105	(1.3%)	1168	(14.5%)
Cardiogenic Shock	4	(.04%)	35	(.44%)
Reinfarction	0	(0%)	5	(.06%)
Cardiac Arrest	5	(.06%)	28	(.34%)
Heart Block (> first degree)	5	(.06%)	143	(1.7%)
Cardiac Failure	1	(.01%)	233	(2.9%)
Arrhythmias	3	(.04%)	22	(.27%)
Bronchospasm	1	(.01%)	50	(.62%)

*Full dosage was 10 mg and some patients received less than 10 mg but more than 5 mg.

During postmarketing experience with TENORMIN, the following have been reported in temporal relationship to the use of the drug: elevated liver enzymes and/or bilirubin, impotence, Peyronie's disease, psoriasiform rash, reversible alopecia, and thrombocytopenia. TENORMIN, like other beta blockers, has been associated with the development of antinuclear antibodies (ANA) and lupus syndrome.

POTENTIAL ADVERSE EFFECTS: In addition, a variety of adverse effects have been reported with other beta-adrenergic blocking agents, and may be considered potential adverse effects of TENORMIN.

Hematologic: Agranulocytosis, purpura.

Allergic: Fever, combined with aching and sore throat, laryngospasm, and respiratory distress.

Central Nervous System: Reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation of time and place; short-term memory loss; emotional lability with slightly clouded sensorium; and, decreased performance on neuropsychometrics.

Gastrointestinal: Mesenteric arterial thrombosis, ischemic colitis.

Other: Erythematous rash, Raynaud's phenomenon.

Miscellaneous: There have been reports of skin rashes and/or dry eyes associated with the use of beta-adrenergic blocking drugs. The reported incidence is small, and in most cases, the symptoms have cleared when treatment was withdrawn. Discontinuance of the drug should be considered if any such reaction is not otherwise explicable. Patients should be closely monitored following cessation of therapy. (SEE DOSAGE AND ADMINISTRATION.)

The oculomucocutaneous syndrome associated with the beta blocker practolol has not been reported with TENORMIN. Furthermore, a number of patients who had previously demonstrated established practolol reactions were transferred to TENORMIN therapy with subsequent resolution or quiescence of the reaction.

OVERDOSAGE: Overdosage with TENORMIN has been reported with patients surviving acute doses as high as 5 g. One death was reported in a man who may have taken as much as 10 g acutely.

The predominant symptoms reported following TENORMIN overdose are lethargy, disorder of respiratory drive, wheezing, sinus pause, and bradycardia. Additionally, common effects associated with overdosage of any beta-adrenergic blocking agent and which might also be expected in TENORMIN overdose are congestive heart failure, hypotension, bronchospasm, and/or hypoglycemia.

Treatment of overdose should be directed to the removal of any unabsorbed drug by induced emesis, gastric lavage, or administration of activated charcoal. TENORMIN can be removed from the general circulation by hemodialysis. Other treatment modalities should be employed at the physician's discretion and may include:

BRADYCARDIA: Atropine intravenously. If there is no response to vagal blockade, give isoproterenol cautiously. In refractory cases, a transvenous cardiac pacemaker may be indicated.

HEART BLOCK (SECOND OR THIRD DEGREE): Isoproterenol or transvenous cardiac pacemaker.

CARDIAC FAILURE: Digitalize the patient and administer a diuretic. Glucagon has been reported to be useful.

HYPOTENSION: Vasopressors such as dopamine or norepinephrine (levarterenol). Monitor blood pressure continuously.

BRONCHOSPASM: A $beta_2$ stimulant such as isoproterenol or terbutaline and/or aminophylline.

HYPOGLYCEMIA: Intravenous glucose.

Based on the severity of symptoms, management may require intensive support care and facilities for applying cardiac and respiratory support.

DOSAGE AND ADMINISTRATION: Hypertension: The initial dose of TENORMIN is 50 mg given as one tablet a day either alone or added to diuretic therapy. The full effect of this dose will usually be seen within one to two weeks. If an optimal response is not achieved, the dosage should be increased to TENORMIN 100 mg given as one tablet a day. Increasing the dosage beyond 100 mg a day is unlikely to produce any further benefit.

TENORMIN may be used alone or concomitantly with other antihypertensive agents including thiazide-type diuretics, hydralazine, prazosin, and alpha-methyldopa.

Angina Pectoris: The initial dose of TENORMIN is 50 mg given as one tablet a day. If an optimal response is not achieved within one week, the dosage should be increased to TENORMIN 100 mg given as one tablet a day. Some patients may require a dosage of 200 mg once a day for optimal effect.

Twenty-four hour control with once daily dosing is achieved by giving doses larger than necessary to achieve an immediate maximum effect. The maximum early effect on exercise tolerance occurs with doses of 50 to 100 mg, but at these doses the effect at 24 hours is attenuated, averaging about 50% to 75% of that observed with once a day oral doses of 200 mg.

Acute Myocardial Infarction: In patients with definite or suspected acute myocardial infarction, treatment with TENORMIN I.V. Injection should be initiated as soon as possible after the patient's arrival in the hospital and after eligibility is established. Such treatment should be initiated in a coronary care or similar unit immediately after the patient's hemodynamic condition has stabilized. Treatment should begin with the intravenous administration of 5 mg TENORMIN over 5 minutes followed by another 5 mg intravenous injection 10 minutes later. TENORMIN I.V. Injection should be administered under carefully controlled conditions including monitoring of blood pressure, heart rate, and electrocardiogram. Dilutions of TENORMIN I.V. Injection in Dextrose Injection USP, Sodium Chloride Injection USP, or Sodium Chloride and Dextrose Injection may be used. These admixtures are stable for 48 hours if they are not used immediately.

In patients who tolerate the full intravenous dose (10 mg), TENORMIN Tablets 50 mg should be initiated 10 minutes after the last intravenous dose followed by another 50 mg oral dose 12 hours later. Thereafter, TENORMIN can be given orally either 100 mg once daily or 50 mg twice a day for a further 6-9 days or until discharge from the hospital. If bradycardia or hypotension requiring treatment or any other untoward effects occur, TENORMIN should be discontinued.

Data from other beta blocker trials suggest that if there is any question concerning the use of IV beta blocker or clinical estimate that there is a contraindication, the IV beta blocker may be eliminated and patients fulfilling the safety criteria may be given TENORMIN Tablets 50 mg twice daily or 100 mg once a day for at least seven days (if the IV dosing is excluded).

Although the demonstration of efficacy of TENORMIN is based entirely on data from the first seven postinfarction days, data from other beta blocker trials suggest that treatment with beta blockers that are effective in the postinfarction setting may be continued for one to three years if there are no contraindications.

TENORMIN is an additional treatment to standard coronary care unit therapy.

Elderly Patients or Patients with Renal Impairment: TENORMIN is excreted by the kidneys; consequently dosage should be adjusted in cases of severe impairment of renal function. Some reduction in dosage may also be appropriate for the elderly, since decreased kidney function is a physiologic consequence of aging. Atenolol excretion would be expected to decrease with advancing age.

No significant accumulation of TENORMIN occurs until creatinine clearance falls below 35 mL/min/1.73m^2. Accumulation of atenolol and prolongation of its half-life were studied in subjects with creatinine clearance between 5 and 105 mL/min. Peak plasma levels were significantly increased in subjects with creatinine clearances below 30 mL/min.

The following maximum oral dosages are recommended for elderly, renally-impaired patients and for patients with renal impairment due to other causes:

Creatinine Clearance (mL/min/1.73m^2)	Atenolol Elimination Half-Life (h)	Maximum Dosage
15-35	16-27	50 mg daily
<15	>27	25 mg daily

Some renally-impaired or elderly patients being treated for hypertension may require a lower starting dose of TENORMIN: 25 mg given as one tablet a day. If this 25 mg dose is used, assessment of efficacy must be made carefully. This should include measurement of blood pressure just prior to the next dose ("trough" blood pressure) to ensure that the treatment effect is present for a full 24 hours.

Although a similar dosage reduction may be considered for elderly and/or renally-impaired patients being treated for indications other than hypertension, data are not available for these patient populations.

Patients on hemodialysis should be given 25 mg or 50 mg after each dialysis; this should be done under hospital supervision as marked falls in blood pressure can occur.

Cessation of Therapy in Patients with Angina Pectoris: If withdrawal of TENORMIN therapy is planned, it should be achieved gradually and patients should be carefully observed and advised to limit physical activity to a minimum.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

HOW SUPPLIED: TENORMIN Tablets: Tablets of 25 mg atenolol, NDC 0310-0107 (round, flat, uncoated white tablets with "T" debossed on one side and 107 debossed on the other side) are supplied in bottles of 100 tablets.

Tablets of 50 mg atenolol, NDC 0310-0105 (round, flat, uncoated white tablets identified with ICI debossed on one side and 105 debossed on the other side, bisected) are supplied in bottles of 100 tablets and 1000 tablets, and unit dose packages of 100 tablets. These tablets are distributed by ICI Pharma.

Tablets of 100 mg atenolol, NDC 0310-0101 (round, flat, uncoated white tablets with ICI debossed on one side and 101 debossed on the other side) are supplied in bottles of 100 tablets and unit dose packages of 100 tablets. These tablets are distributed by ICI Pharma.

Store at controlled room temperature, 15°-30°C (59°-86°F). Dispense in well-closed, light resistant containers.

TENORMIN I.V. Injection: TENORMIN I.V. Injection, NDC 0310-0108, is supplied as 5 mg atenolol in 10 mL ampules of isotonic citrate-buffered aqueous solution.

Protect from light. Keep ampules in outer packaging until time of use. Store at room temperature.

REV W 11/91

ICI Pharma

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Wilmington, Delaware 19897 USA

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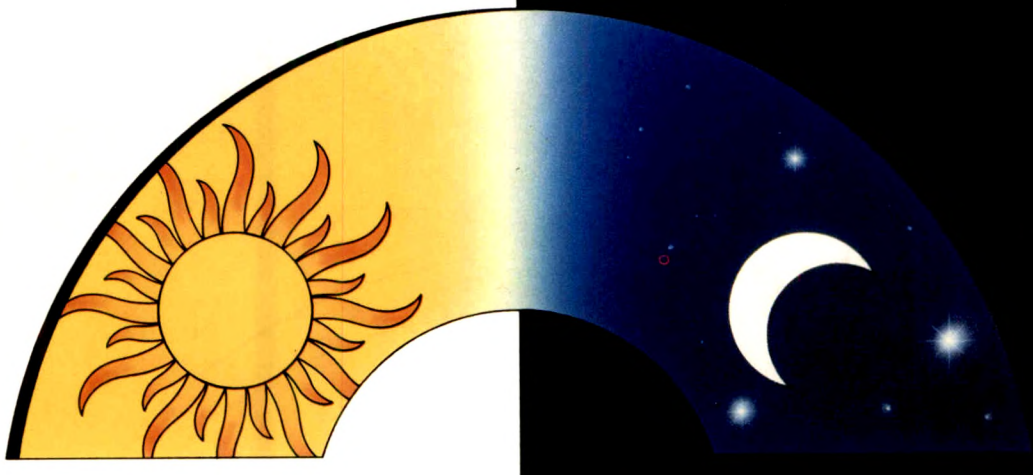
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ALL DAY ALL NIGHT

ALTACE™

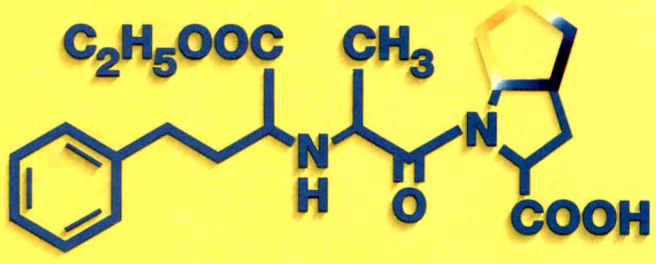
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24-HOUR BLOOD PRESSURE CONTROL

Please see brief summary of prescribing information on last page.

ALL DAY

Unique Cyclopentane Ring for Distinctive Pharmacology



Longest serum half-life

13 to 17 hours

High ACE affinity

Binds readily to enzyme and dissociates slowly[1]

Enhanced tissue penetration

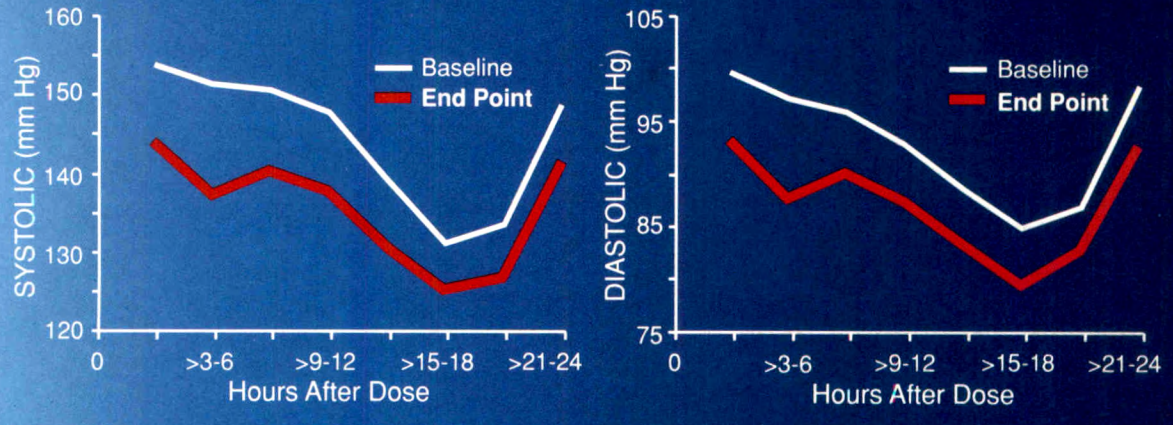
Markedly reduced ACE activity in both human serum and tissue for effective blood pressure control[2]

* In some patients treated once daily, the antihypertensive effect may diminish toward the end of the dosing interval.

Please see brief summary of prescribing information on last page.

ALL NIGHT

24-Hour Blood Pressure Control with a Once-a-Day Dose*



Mean 24-hour ambulatory blood pressures in 67 patients at baseline and after 4 weeks of therapy. (Adapted from McCarron.[3])

Usual starting dose—
2.5 mg once-a-day

ALTACE™
ramipril

ALL DAY/ALL NIGHT

ALTACE™ ramipril

Usual Starting Dose–2.5 mg Once-a-Day

Available in Easy-to-Swallow Capsules



1.25 mg | 2.5 mg | 5 mg | 10 mg

BRIEF SUMMARY

USE IN PREGNANCY

When used in pregnancy during the second and third trimesters, ACE inhibitors can cause injury and even death to the developing fetus. When pregnancy is detected, ALTACE should be discontinued as soon as possible. **See WARNINGS: Fetal/neonatal morbidity and mortality.**

ALTACE is available in potencies of 1.25 mg, 2.5 mg, 5 mg, and 10 mg in color-coded, hard gelatin capsules.

INDICATIONS AND USAGE: ALTACE is indicated for the treatment of hypertension. It may be used alone or in combination with thiazide diuretics.

In using ALTACE, consideration should be given to the fact that another angiotensin converting enzyme inhibitor, captopril, has caused agranulocytosis, particularly in patients with renal impairment or collagen-vascular disease. Available data are insufficient to show that ALTACE does not have a similar risk. (See WARNINGS.)

CONTRAINDICATIONS: ALTACE is contraindicated in patients who are hypersensitive to this product and in patients with history of angioneurotic edema.

WARNINGS: ***Angioedema:*** Angioedema of the face, extremities, lips, tongue, glottis, and larynx has been reported in patients treated with angiotensin converting enzyme inhibitors. Angioedema associated with laryngeal edema can be fatal. If laryngeal stridor or angioedema of the face, tongue, or glottis occurs, treatment with ALTACE should be discontinued and appropriate therapy instituted immediately. **Where there is involvement of the tongue, glottis, or larynx, likely to cause airway obstruction, appropriate therapy, e.g., subcutaneous epinephrine solution 1:1,000 (0.3 ml to 0.5 ml) should be promptly administered.** (See ADVERSE REACTIONS.)

Hypotension: ALTACE can cause symptomatic hypotension, after either the initial dose or a later dose when the dosage has been increased. Like other ACE inhibitors, ramipril has been only rarely associated with hypotension in uncomplicated hypertensive patients. Symptomatic hypotension is most likely to occur in patients who have been volume- and/or salt-depleted as a result of prolonged diuretic therapy, dietary salt restriction, dialysis, diarrhea, or vomiting. Volume and/or salt depletion should be corrected before initiating therapy with ALTACE.

In patients with congestive heart failure, with or without associated renal insufficiency, ACE inhibitor therapy may cause excessive hypotension, which may be associated with oliguria or azotemia and, rarely, with acute renal failure and death. In such patients, ALTACE therapy should be started under close medical supervision; they should be followed closely for the first 2 weeks of treatment and whenever the dose of ramipril or diuretic is increased.

If hypotension occurs, the patient should be placed in a supine position and, if necessary, treated with intravenous infusion of physiological saline. ALTACE treatment usually can be continued following restoration of blood pressure and volume.

Neutropenia/Agranulocytosis: Another angiotensin converting enzyme inhibitor, captopril, has been shown to cause agranulocytosis and bone marrow depression, rarely in uncomplicated patients, but more frequently in patients with renal impairment, especially if they also have a collagen-vascular disease such as systemic lupus erythematosus or scleroderma. Available data from clinical trials of ramipril are insufficient to show that ramipril does not cause agranulocytosis at similar rates. Monitoring of white blood cell counts should be considered in patients with collagen-vascular disease, especially if the disease is associated with impaired renal function.

Fetal/Neonatal Morbidity and Mortality: ACE inhibitors can cause fetal and neonatal morbidity and death when administered to pregnant women. More than 100 cases have been reported in the world literature. When pregnancy is detected, ACE inhibitors should be discontinued as soon as possible.

The use of ACE inhibitors during the second and third trimesters of pregnancy has been associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible and irreversible renal failure, and death. Oligohydramnios has also been reported, presumably resulting from decreased fetal renal function; oligohydramnios in this setting has been associated with fetal limb contractures, craniofacial deformation, and hypoplastic lung development. Prematurity, intrauterine growth retardation, and patent ductus arteriosus have also been reported, although it is not clear whether these occurrences were due to the ACE-inhibitor exposure.

These adverse effects do not appear to have resulted from intrauterine ACE-inhibitor exposure that has been limited to the first trimester. Mothers whose embryos and fetuses are exposed to ACE inhibitors only during the first trimester should be so informed. Nonetheless, when patients become pregnant, physicians should make every effort to discontinue the use of ALTACE as soon as possible.

Rarely (probably less often than once in every thousand pregnancies), no alternative to ACE inhibitors will be found. In these rare cases, the mothers should be apprised of the potential hazards to their fetuses, and serial ultrasound examination should be performed to assess the intra-amniotic environment.

If oligohydramnios is observed, ALTACE should be discontinued unless it is considered lifesaving for the mother. Contraction stress testing (CST), a non-stress test (NST), or biophysical profiling (BPP) may be appropriate depending upon the week of pregnancy. Patients and physicians should be aware, however, that oligohydramnios may not be apparent until after the fetus has sustained irreversible injury.

Infants with histories of *in utero* exposure to ACE inhibitors should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion. Exchange transfusion or dialysis may be required as means of reversing hypotension and/or substituting for disordered renal function. ALTACE, which crosses the placenta, can be removed from the neonatal circulation by these means, but limited experience has not shown that such removal is central to the treatment of these infants.

No teratogenic effects of ALTACE were seen in studies of pregnant rats, rabbits, and cynomolgus monkeys. On a mg/kg basis, the doses used were up to 2,500 times (in rats), 6.25 times (in rabbits), and 1,250 times (in monkeys) the maximum recommended human dose.

PRECAUTIONS: ***General:*** *Impaired Renal Function:* As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients with severe congestive heart failure whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with angiotensin converting enzyme inhibitors, including ALTACE, may be associated with oliguria and/or progressive azotemia and (rarely) with acute renal failure and/or death. In hypertensive patients with unilateral or bilateral renal artery stenosis, increases in blood urea nitrogen and serum creatinine may occur. Experience with another angiotensin converting enzyme inhibitor suggests that these increases are usually reversible upon discontinuation of ALTACE and/or diuretic therapy. In such patients renal function should be monitored during the first few weeks of therapy. Some hypertensive patients with no apparent pre-existing renal vascular disease have developed increases in blood urea nitrogen and serum creatinine, usually minor and transient, especially when ALTACE has been given concomitantly with a diuretic. This is more likely to occur in patients with pre-existing renal impairment. Dosage reduction of ALTACE and/or discontinuation of the diuretic may be required.

Evaluation of the hypertensive patient should always include assessment of renal function.

Hyperkalemia: In clinical trials, hyperkalemia (serum potassium greater than 5.7 mEq/L) occurred in approximately 1% of hypertensive patients receiving ALTACE. In most cases, these were isolated values, which resolved despite continued therapy. None of these patients was discontinued from the trials because of hyperkalemia. Risk factors for the development of hyperkalemia include renal insufficiency, diabetes mellitus, and the concomitant use of potassium-sparing diuretics, potassium supplements, and/or potassium-containing salt substitutes, which should be used cautiously, if at all, with ALTACE. (See DRUG INTERACTIONS.)

Cough: Cough has been reported with the use of ACE inhibitors. Characteristically, the cough is nonproductive, persistent and resolves after discontinuation of therapy. ACE inhibitor-induced cough should be considered as part of the differential diagnosis of cough.

Impaired Liver Function: Since ramipril is primarily metabolized by hepatic esterases to its active moiety, ramiprilat, patients with impaired liver function could develop markedly elevated plasma levels of ramipril. No formal pharmacokinetic studies have been carried out in hypertensive patients with impaired liver function.

Surgery/Anesthesia: In patients undergoing surgery or during anesthesia with agents that produce hypotension, ramipril may block angiotensin II formation that would otherwise occur secondary to compensatory renin release. Hypotension that occurs as a result of this mechanism can be corrected by volume expansion.

Information for Patients: *Angioedema:* Angioedema, including laryngeal edema, can occur with treatment with ACE inhibitors, especially following the first dose. Patients should be so advised and told to report immediately any signs or symptoms suggesting angioedema (swelling of face, eyes, lips, tongue, or difficulty in breathing) and to take no more drug until they have consulted with the prescribing physician.

Symptomatic Hypotension: Patients should be cautioned that lightheadedness can occur, especially during the first days of therapy, and it should be reported. Patients should be told that if syncope occurs, ALTACE™ (ramipril) should be discontinued until the physician has been consulted.

All patients should be cautioned that inadequate fluid intake or excessive perspiration, diarrhea, or vomiting can lead to an excessive fall in blood pressure, with the same consequences of lightheadedness and possible syncope.

Hyperkalemia: Patients should be told not to use salt substitutes containing potassium without consulting their physician.

Neutropenia: Patients should be told to promptly report any indication of infection (e.g., sore throat, fever), which could be a sign of neutropenia.

Pregnancy: Female patients of childbearing age should be told about the consequences of second- and third-trimester exposure to ACE inhibitors, and they should also be told that these consequences do not appear to have resulted from intrauterine ACE-inhibitor exposure that has been limited to the first trimester. These patients should also be asked to report pregnancies to their physicians as soon as possible.

Drug Interactions: *With Diuretics:* Patients on diuretics, especially those in whom diuretic therapy was recently instituted, may occasionally experience an excessive reduction of blood pressure after initiation of therapy with ALTACE. The possibility of hypotensive effects with ALTACE can be minimized by either discontinuing the diuretic or increasing the salt intake prior to initiation of treatment with ALTACE. If this is not possible, the starting dose should be reduced.

With Potassium Supplements and Potassium-Sparing Diuretics: ALTACE can attenuate potassium loss caused by thiazide diuretics. Potassium-sparing diuretics (spironolactone, amiloride, triamterene, and others) or potassium supplements can increase the risk of hyperkalemia. Therefore, if concomitant use of such agents is indicated, they should be given with caution, and the patient's serum potassium should be monitored frequently.

With Lithium: Increased serum lithium levels and symptoms of lithium toxicity have been reported in patients receiving ACE inhibitors during therapy with lithium. These drugs should be coadministered with caution, and frequent monitoring of serum lithium levels is recommended. If a diuretic is also used, the risk of lithium toxicity may be increased.

Other: Neither ALTACE nor its metabolites have been found to interact with food, digoxin, or antacid.

Carcinogenesis, Mutagenesis, Impairment of Fertility: No evidence of a tumorigenic effect was found when ramipril was given by gavage to rats (up to 500 mg/kg/day for 24 months) or to mice (up to 1,000 mg/kg/day for 18 months). Dosages greatly in excess of those recommended for humans produced hypertrophy of the renal juxtaglomerular apparatus in mice, rats, dogs, and monkeys. No mutagenic activity was detected in the Ames test in bacteria, the micronucleus test in mice, unscheduled DNA synthesis in a human cell line, or a forward gene-mutation assay in a Chinese hamster ovary cell line. Several metabolites and degradation products of ramipril were also negative in the Ames test. A study in rats with dosages as great as 500 mg/kg/day did not produce adverse effects on fertility.

Pregnancy: **Pregnancy Categories C (first trimester) and D (second and third trimesters): See WARNINGS: Fetal/neonatal morbidity and mortality.**

Nursing Mothers: Ingestion of a single 10 mg oral dose of ALTACE resulted in undetectable amounts of ramipril and its metabolites in breast milk. However, because multiple doses may produce low milk concentrations that are not predictable from single doses, ALTACE should not be administered to nursing mothers.

Geriatric Use: Of the total number of patients who received ramipril in US clinical studies of ALTACE 11.0% were 65 and over while 0.2% were 75 and over. No overall differences in effectiveness or safety were observed between these patients and younger patients, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

One pharmacokinetic study conducted in hospitalized elderly patients indicated that peak ramiprilat levels and area under the plasma concentration time curve (AUC) for ramiprilat are higher in older patients.

Pediatric Use: Safety and effectiveness in children has not been established.

ADVERSE REACTIONS: ALTACE has been evaluated for safety in over 4,000 patients with hypertension; of these, 1,230 patients were studied in US controlled trials, and 1,107 were studied in foreign controlled trials. Almost 700 of these patients were treated for at least one year. The overall incidence of reported adverse events was similar in ALTACE and placebo patients. The most frequent clinical side effects (possibly or probably related to study drug) reported by patients receiving ALTACE in US placebo-controlled trials were: headache (5.4%), "dizziness" (2.2%) and fatigue or asthenia (2.0%), but only the last was more common in ALTACE patients than in patients given placebo. Generally, the side effects were mild and transient, and there was no relation to total dosage within the range of 1.25 to 20 mg. Discontinuation of therapy because of a side effect was required in approximately 3% of US patients treated with ALTACE. The most common reasons for discontinuation were: cough (1.0%), "dizziness" (0.5%), and impotence (0.4%).

The side effects considered possibly or probably related to study drug that occurred in US placebo-controlled trials in more than 1% of patients treated with ALTACE are shown below.

PATIENTS IN US PLACEBO-CONTROLLED STUDIES

	Altace (N = 651)		Placebo (N = 286)	
	n	%	n	%
Headache	35	5.4	17	5.9
"Dizziness"	14	2.2	9	3.1
Asthenia (Fatigue)	13	2.0	2	0.7
Nausea/ Vomiting	7	1.1	3	1.0

In placebo-controlled trials, there was also an excess of upper respiratory infection and flu syndrome in the ramipril group. As these studies were carried out before the relationship of cough to ACE inhibitors was recognized, some of these events may represent ramipril-induced cough. In a later 1-year study, increased cough was seen in almost 12% of ramipril patients, with about 4% of these patients requiring discontinuation of treatment. Other adverse experiences reported in controlled clinical trials (in less than 1% of ramipril patients), or rarer events seen in postmarketing experience, include the following (In some, a causal relationship to drug use is uncertain.):

Cardiovascular: Symptomatic hypotension (reported in 0.5% of patients in US trials) (see PRECAUTIONS and WARNINGS), syncope (not reported in US trials), angina pectoris, arrhythmia, chest pain, palpitations, myocardial infarction, and cerebrovascular events.

Renal: Some hypertensive patients with no apparent pre-existing renal disease have developed minor, usually transient, increases in blood urea nitrogen and serum creatinine when taking ALTACE, particularly when ALTACE was given concomitantly with a diuretic. (See WARNINGS.)

Angioneurotic Edema: Angioneurotic edema has been reported in 0.3% of patients in US clinical trials. (See WARNINGS.)

Cough: A tickling, dry, persistent, nonproductive cough has been reported with the use of ACE inhibitors. Approximately 1% of patients treated with ALTACE have required discontinuation because of cough. The cough disappears shortly after discontinuation of treatment. (See PRECAUTIONS.)

Gastrointestinal: Abdominal pain (sometimes with enzyme changes suggesting pancreatitis), anorexia, constipation, diarrhea, dry mouth, dyspepsia, dysphagia, gastroenteritis, nausea, increased salivation, taste disturbance, and vomiting.

Dermatologic: Apparent hypersensitivity reactions (manifested by dermatitis, pruritus, or rash, with or without fever), photosensitivity, and purpura.

Neurologic and Psychiatric: Anxiety, amnesia, convulsions, depression, hearing loss, insomnia, nervousness, neuralgia, neuropathy, paresthesia, somnolence, tinnitus, tremor, vertigo, and vision disturbances.

Fetal/Neonatal Morbidity and Mortality: See WARNINGS: Fetal/neonatal morbidity and mortality.

Other: arthralgia, arthritis, dyspnea, edema, epistaxis, impotence, increased sweating, malaise, myalgia, and weight gain.

Clinical Laboratory Test Findings: *Creatinine and Blood Urea Nitrogen:* Increases in creatinine levels occurred in 1.2% of patients receiving ALTACE alone, and in 1.5% of patients receiving ALTACE and a diuretic. Increases in blood urea nitrogen levels occurred in 0.5% of patients receiving ALTACE alone and in 3% of patients receiving ALTACE with a diuretic. None of these increases required discontinuation of treatment. Increases in these laboratory values are more likely to occur in patients with renal insufficiency or those pretreated with a diuretic and, based on experience with other ACE inhibitors, would be expected to be especially likely in patients with renal artery stenosis. (See PRECAUTIONS and WARNINGS.)

Since ramipril decreases aldosterone secretion, elevation of serum potassium can occur. Potassium supplements and potassium-sparing diuretics should be given with caution, and the patient's serum potassium should be monitored frequently. (See PRECAUTIONS and WARNINGS.)

Hemoglobin and Hematocrit: Decreases in hemoglobin or hematocrit (a low value and a decrease of 5 g/dl or 5% respectively) were rare, occurring in 0.4% of patients receiving ALTACE alone and in 1.5% of patients receiving ALTACE plus a diuretic. No US patients discontinued treatment because of decreases in hemoglobin or hematocrit.

Other (causal relationships unknown): Clinically important changes in standard laboratory tests were rarely associated with ALTACE administration. Elevations of liver enzymes, serum bilirubin, uric acid, and blood glucose have been reported, as have scattered incidents of leukopenia, eosinophilia, and proteinuria. In US trials, less than 0.2% of patients discontinued treatment for laboratory abnormalities: all of these were cases of proteinuria or abnormal liver-function tests.

OVERDOSAGE: Human overdoses of ramipril have not been reported, but the most common manifestation of human ramipril overdosage is likely to be hypotension. Because the hypotensive effect of ramipril is achieved through vasodilation and effective hypovolemia, it is reasonable to treat ramipril overdose by infusion of normal saline solution.

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Q65106-392

The American Journal of Cardiology

JUNE 1, 1992, VOL. 69, NO. 17

Frequency and Outcome of Chest Pain After Two New Coronary Interventions (Atherectomy and Stenting)

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Between June 1988 and July 1991, 464 new device interventions (Palmaz-Schatz stent or Simpson directional atherectomy) were performed in 410 patients. Chest pain occurred within 72 hours after the procedure in 94 patients (23%). All patients were evaluated with electrocardiograms and cardiac isoenzymes on the day after the procedure, and urgent repeat coronary angiography was performed in 29 chest pain patients (31%). Whereas all 14 patients with abnormal findings on repeat angiography had electrocardiographic changes, 6 of the 20 restudied patients (30%) with electrocardiographic changes had no angiographic explanation for chest pain. Non-Q-wave myocardial infarction occurred in 22 patients (5%) (10 of 35 [29%] with chest pain and electrocardiographic changes, 3 of 44 [7%] with chest pain and no electrocardiographic change, and 9 of 316 [3%] without chest pain). Factors associated with chest pain after new device intervention included a decreased residual percent stenosis ($p = 0.05$), incomplete revascularization ($p = 0.005$) and the presence of multivessel disease ($p = 0.001$). Vessel dissection after stenting but not atherectomy was associated with postprocedure chest pain.

Chest pain is common (23%) after new device intervention. Electrocardiographic changes are a sensitive marker of angiographic abnormality and confer a higher risk of non-Q-wave myocardial infarction, but no increase of in-hospital mortality. Determinants of postprocedure chest pain are lower residual percent stenosis, incomplete revascularization and the presence of multivessel disease. Patients with chest pain but no electrocardiographic changes early after successful stent placement or atherectomy need not routinely undergo urgent recatheterization.

(Am J Cardiol 1992;69:1379–1382)

In recent years, >20 newer devices for performing percutaneous coronary revascularization entered clinical testing with the hope of improving the acute success and long-term efficacy of balloon angioplasty.[1,2] Two of these devices (the Palmaz-Schatz intracoronary stent [Johnson and Johnson Interventional Systems, Warren, New Jersey] and the Simpson directional coronary atherectomy catheter [Devices for Vascular Intervention, Inc., Redwood City, California]) have each been used in >1,000 patients. Investigations have contributed to understanding the mechanism of action, technical use, limitations, and acute and long-term results of these devices.[3–8] Although analyses of patients with chest pain after percutaneous transluminal coronary angioplasty have been reported,[9–11] no analysis has yet focused on the frequency and causes of recurrent chest pain after treatment with these 2 devices. Such pain may herald abrupt closure, as reported after percutaneous transluminal coronary angioplasty,[12,13] but may simply reflect local coronary artery trauma. Distinguishing between these 2 causes of chest pain is crucial in selecting optimal management. Therefore, we reviewed retrospectively the clinical course, management and outcome in patients with in-hospital chest pain after percutaneous coronary revascularization by 1 of these 2 new device interventions.

METHODS

Study patients: Over the 3-year period between June 1988 and July 1991, 464 new device interventions were performed in 410 patients at Beth Israel Hospital. Of the 464 interventions, 226 were directional coronary atherectomies, and 238 were placement of intracoronary stents. All patients routinely had electrocardiograms before, immediately after and on the morning af-

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TABLE I Postprocedure Chest Pain and Electrocardiogram as Predictors of Adverse Outcomes

	In-Hospital Mortality	Non-Q-Wave MI (%)	Repeat Angiography (%)	Abnormal Angiography (%)	Repeat Intervention (%)
CP/+ECG	0	10/35 (29)	20/50 (39)	14/20 (70)	*8/20 (40)*
CP/−ECG	0	3/44 (7)	9/44 (20)	0/9 (0)	0
No CP	0	9/316 (3)	—	—	0

*75% of patients who needed repeat intervention had electrocardiographic ST-segment depression or elevation ≥ 1 mm.
CP = chest pain; ECG = electrocardiogram; MI = myocardial infarction.

TABLE II Determinants of Postprocedure Chest Pain

Variable	Percent Prevalence	RR of CP	p Value
Incomplete revascularization	—	—	0.005
Multivessel disease	—	—	0.001
Lower residual percent stenosis	—	—	0.05
Prior restenosis	—	—	0.68
Pathology (DCA only, n = 226)			
Adventitia	28%	0.91	0.37
Media	66%	1.08	0.31
Thrombus	41%	0.89	0.20
Plaque	95%	0.81	0.37
Intimal hyperplasia	57%	1.04	0.63
Morphology (all lesions, n = 464)			
Eccentric lesion	52%	0.97	0.63
Artery calcification	10%	1.03	0.57
DCA	18%	1.21	0.07
Stents	3.5%	0.74	0.10
Vessel dissection	11%	1.21	0.02
DCA	11%	1.05	0.68
Stents	11%	1.40	0.01
Artery size	—	—	0.44
Postprocedure absolute luminal diameter	—	—	0.58

CP = chest pain; DCA = directional coronary atherectomy; RR = relative risk.

ter the procedure. Electrocardiograms were also obtained during episodes of postprocedure chest pain. Single measurements of serum creatinine phosphokinase and creatinine phosphokinase isoenzymes were performed routinely on the morning after the procedure, and serial cardiac isoenzymes were obtained in patients reporting postprocedure chest pain. Non-Q-wave myocardial infarction was defined as serum creatine phosphokinase >200 with MB isoenzymes >5% (10 U).

Repeat coronary angiography was performed in patients with postprocedure chest pain at the discretion of the attending physician and interventional cardiologist. Subsequent revascularization procedures were performed as dictated by the findings at the time of repeat angiography. Histopathologic data were obtained in all directional coronary atherectomy specimens.

Follow-up: Follow-up for all patients consisted of standard Bruce protocol thallium exercise stress testing at 6, 12, and 24 weeks after the procedure. Follow-up coronary angiography was performed routinely at ≤24 weeks, as dictated by recurrent chest pain or positive exercise study.

Statistical analysis: Relative risks were derived based on differences in certain variables between patients with and without chest pain. These differences were tested using chi-square analysis. Student's *t* test was performed to assess differences between continuous variables. A p value ≤0.05 was considered significant.

RESULTS

Patient population: Chest pain occurred within 72 hours in 94 of 410 patients (23%) after new device percutaneous revascularization (21% after directional coronary atherectomy, and 24% after intracoronary stent placement).

Angiographic evaluation: Twenty-nine of 94 patients (31%) with chest pain after percutaneous coronary revascularization underwent repeat coronary angiography during the same hospitalization. Patients undergoing repeat coronary angiography were divided in groups based on electrocardiographic findings at the time of chest pain. Group 1 comprised 9 patients with ST-segment elevation or depression ≥1 mm, all of whom had repeat coronary angiography. Group 2 included 41 patients with nonspecific electrocardiographic changes during chest pain, 11 (26%) of whom underwent repeat coronary angiography. Group 3 included 44 patients with no electrocardiographic changes during chest pain, 9 (21%) of whom underwent repeat coronary angiography.

Fourteen of the 29 patients who underwent repeat angiography had abnormal angiograms (abrupt vessel closure in 1, sidebranch occlusion in 3, distal embolization in 3, and untreated distal stenosis in 1). Two patients had severe coronary artery disease in another coronary artery, with a widely patent vessel at the site of the original intervention.

All 14 patients with abnormal angiograms had electrocardiographic changes with chest pain. Of the 50 patients who had electrocardiographic changes, 20 had repeat angiography (14 [70%] of whom had abnormal coronary angiograms). Of the 8 patients who needed additional intervention, 6 (75%) had ST-segment shifts of 1 mm with recurrent chest pain (Table I). Therefore, the sensitivity (100%) of the electrocardiographic change for predicting angiographic abnormality exceeds the specificity (60%).

Decreased postprocedure residual percent stenosis ($p = 0.05$), the presence of multivessel disease ($p = 0.001$), and incomplete revascularization ($p = 0.005$) were each associated with postprocedure chest pain after new device intervention. Angiographically evident dissection of the coronary artery was associated with the occurrence of postprocedure chest pain after stenting ($p = 0.01$), but not atherectomy ($p = 0.68$). There was also a trend ($p = 0.07$) toward association of artery cal-

cification with postprocedure chest pain in directional coronary atherectomy patients (Table II). Patients with chest pain after intracoronary stent placement (but not directional coronary atherectomy) had less subsequent angiographic restenosis ($p = 0.016$) than did those without chest pain.

Laboratory and pathology analysis: There were no Q-wave myocardial infarctions, but cardiac isoenzyme elevation (MB isoform elevation >5% of total creatinine phosphokinase) consistent with non-Q-wave myocardial infarction occurred in 22 patients (5%). The average creatine phosphokinase was 553 IU/ml with 10% MB isoform (>400 IU/ml in 12 of 22 patients [55%]). Non-Q-wave myocardial infarctions occurred in 10 of 35 patients (29%) with chest pain and electrocardiographic changes, in 3 of 44 (7%) with chest pain and no electrocardiographic changes, and in 9 of 316 (3%) without chest pain after stent placement or atherectomy (Figure 1).

Histopathologic finding of media and adventitia in the directional coronary atherectomy specimen was not associated with a higher incidence of postprocedure chest pain (Table II).

DISCUSSION

Directional atherectomy and balloon expandable stents are promising new devices for coronary intervention. In centers such as ours, >20% of patients are currently treated with one of these devices instead of, or in conjunction with, conventional percutaneous angioplasty. Optimal postprocedure management of this growing number of patients is critical to the overall success, safety and cost effectiveness of these new technologies. The National Heart, Lung, and Blood Institute Percutaneous Transluminal Coronary Angioplasty Registry reported a 6.8% occurrence of prolonged angina (chest pain persisting longer than usual, or angina unrelieved promptly with sublingual or parenteral nitroglycerin) after percutaneous transluminal coronary angioplasty.[13] Identification of patients whose chest pain represents acute myocardial ischemia rather than local vessel injury ("stretch pain") can often be difficult.[14] Therefore, we included in our analysis all patients reporting chest pain after new device intervention. Chest pain after percutaneous revascularization with these new devices was common (23%) and similar in frequency to that reported after conventional percutaneous coronary balloon angioplasty.[9,10] However, in contrast to the 1 to 2% acute coronary occlusion rate reported after percutaneous transluminal coronary angioplasty, there was only a 0.2% (1 of 410 cases) incidence of acute occlusion with these 2 new devices.[12,15,16]

Angiographic evident dissection occurred infrequently, but was associated with postprocedure chest pain ($p = 0.02$ overall; $p = 0.01$ after stenting; $p = 0.68$ after atherectomy). This same association has also been reported with balloon angioplasty ($p < 0.001$).[9]

Despite the superior acute gain after stenting or atherectomy compared with that after conventional balloon angioplasty, the incidence of postprocedure chest pain (23%), and the number of patients needing further intervention (2% of the total) was similar. It appears likely that much of the other postprocedure chest pain in this series relates to the local vessel trauma associated with producing the low (0 to 10%) residual stenosis seen after stent placement and directional coronary atherectomy.

Basic evaluation of any patient with chest pain after coronary intervention includes a 12-lead electrocardiogram. An electrocardiogram showing changes consistent with ischemia is a sensitive but nonspecific marker for the presence of an angiographic abnormality should repeat coronary angiography be performed. Patients with chest pain but a normal electrocardiogram were not found to have angiographic abnormalities (Table I). Similar prognostic stratification of patients with chest pain and a negative electrocardiogram into a low-risk group for major complications has also been established in outpatients who present for evaluation of symptoms that may represent myocardial ischemia.[17,18] Patients with chest pain and electrocardiographic changes were at fivefold higher risk for sustaining non-Q-wave myo-

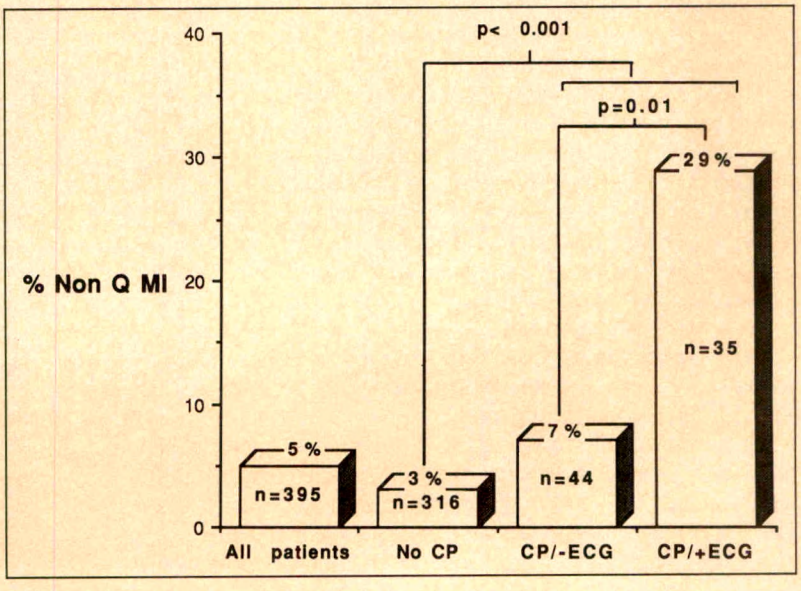


FIGURE 1. Percent occurrence of non-Q-wave myocardial infarction (% Non Q MI) in all patients, those without chest pain (CP), those with pain and no electrocardiographic (ECG) changes, and those with pain and electrocardiographic changes. Difference of non-Q-wave myocardial infarction between patients with and without chest pain was statistically significant ($p < 0.001$), as was that between those with chest pain with and without electrocardiographic changes ($p = 0.01$).

cardial infarction during hospitalization than were those with chest pain and no electrocardiographic changes after new device intervention.

In this series, the occurrence of such non-Q-wave myocardial infarctions was not associated with an apparent increase in hospital mortality. This was contrary to the increased (9.4%) mortality rate reported in patients with non-Q-wave myocardial infarction after percutaneous transluminal coronary angioplasty.[13]

Based on our findings, patients with chest pain and ST-segment shifts of 1 mm should undergo emergency repeat cardiac catheterization, because they are highly likely (88%) to need further intervention. Chest pain with ischemic electrocardiographic changes after conventional balloon angioplasty has similarly been shown to be the strongest predictor ($p < 0.001$) for the need for further intervention.[9] Repeat catheterization is also probably indicated in patients with chest pain and nonspecific electrocardiographic changes (particularly with multivessel disease or incomplete revascularization, or both), even though only 2 of 42 (5%) with such nonspecific electrocardiographic changes needed further intervention. Patients with chest pain but no electrocardiographic changes probably should not undergo repeat angiography. These patients are unlikely to have angiographic abnormality or need repeat intervention, although they still have a twofold higher incidence of non-Q-wave myocardial infarction than that of those with no chest pain (7 vs 3%; $p = 0.02$).

It should be noted that the 2 new devices discussed here are generally used on focally diseased proximal vessels ≥ 3 mm in diameter. Therefore, abrupt closure at the site of interventions is likely to produce diagnostic electrocardiographic changes. However, owing to the excellent angiographic results and low frequency of closure at the treated site with stent placement and directional atherectomy, recurrent intervention was seldom needed at the site of previous intervention. Further intervention was more likely to involve treatment of a branch, distal site or other incompletely revascularized territory. These smaller, more distal or branch lesions may account for the absence of more striking electrocardiographic changes. Well-collateralized or previously occluded vessels may also be electrocardiographically silent, if they occlude abruptly.

Chest pain after intracoronary stent placement was associated ($p = 0.011$) with a lower angiographic restenosis rate at 6-month angiographic follow-up. If a larger postprocedure luminal diameter is associated with a lower incidence of subsequent restenosis, the vessel stretching needed to achieve a 0% or better residual stenosis with the Palmaz-Schatz stent may explain the association between postprocedure chest pain and a lower probability of restenosis at 6 months.[19] However, this same association of postprocedure pain with lower restenosis at 6 months was not found among directional coronary atherectomy patients.

In summary, chest pain appears to be a frequent occurrence after new device intervention. A lower postprocedure percent stenosis, incomplete revascularization and the presence of multivessel disease were associated with chest pain after new device intervention. Angiographically evident dissection was associated with postprocedure chest pain after stent placement. Electrocardiographic changes were sensitive but nonspecific for coronary angiographic abnormalities.

Although patients with chest pain and no electrocardiographic changes may have a slightly higher risk of non-Q-wave myocardial infarction, they need not undergo urgent repeat catheterization, because further intervention was not needed in this group. Chest pain after stent placement is associated with a lower restenosis rate at 6 months, possibly due to greater overdilatation.

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Low incidence of ICB (0.5%)[1-9] when used with IV heparin

ICB rates in clinical trials with Activase® and IV heparin[1-9]

Clinical source	N	% ICB	Reported occurrence (n)
TIMI-II*[1]	3,016	0.4%	13
Pooled data from 8 other studies**[2-9]	3,359	0.6%	19
Total	6,375	0.5%	32

*In the TIMI-II (Thrombolysis in Myocardial Infarction) study, the largest U.S. thrombolytic trial to date, 3,016 patients were treated with IV heparin, aspirin, and 100 mg of Activase®; the occurrence of intracranial hemorrhage was 0.4%.[1]

A cumulative mortality rate of 5.9%[2,10] for a positive effect on survival

Clinical source	N	% mortality	Reported deaths (n)
ASSET†[2]	2,515	7.2%	182
TIMI-II*[10]	3,016	4.8%	146
Total	5,531	5.9%	328

Bleeding is the most common complication of thrombolytic therapy, with intracranial bleeding being the most serious. Activase® is contraindicated in patients with: active internal bleeding, history of cerebrovascular accident, recent (within two months) intracranial or intraspinal surgery or trauma, intracranial neoplasm, arteriovenous malformation or aneurysm, known bleeding diathesis, or severe uncontrolled hypertension. (See WARNINGS section of prescribing information.)

**0.3% reported ICB occurrence in ASSET trial (n=2,515)
†Aspirin was not used in the ASSET trial

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Brief Summary
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INDICATIONS AND USAGE: ACTIVASE® is indicated for use in the management of acute myocardial infarction (AMI) in adults for the lysis of thrombi obstructing coronary arteries, the reduction of infarct size, the improvement of ventricular function following AMI, the reduction of the incidence of congestive heart failure and the reduction of mortality associated with AMI. Treatment should be initiated as soon as possible after the onset of AMI symptoms.
ACTIVASE® is also indicated in the management of acute massive pulmonary embolism (PE) in adults: for the lysis of acute pulmonary emboli, defined as obstruction of blood flow to a lobe or multiple segments of the lungs, and for the lysis of pulmonary emboli accompanied by unstable hemodynamics, i.e., failure to maintain blood pressure without supportive measures. The diagnosis should be confirmed by objective means, such as pulmonary angiography or noninvasive procedures such as lung scanning.

CONTRAINDICATIONS: Because thrombolytic therapy increases the risk of bleeding, ACTIVASE® is contraindicated in the following situations: • Active internal bleeding • History of cerebrovascular accident • Recent (within two months) intracranial or intraspinal surgery or trauma (see WARNINGS) • Intracranial neoplasm, arteriovenous malformation, or aneurysm • Known bleeding diathesis • Severe uncontrolled hypertension.

WARNINGS: Bleeding The most common complication encountered during ACTIVASE® therapy is bleeding. The type of bleeding associated with thrombolytic therapy can be divided into two broad categories: • Internal bleeding involving the gastrointestinal or genitourinary tract, or retroperitoneal or intracranial sites • Superficial or surface bleeding, observed mainly at invaded or disturbed sites (e.g., sites of venous cutdown, arterial puncture, recent surgical intervention).

Concomitant use of heparin anticoagulation may contribute to bleeding. Some hemorrhagic episodes occurred one or more days after the effects of ACTIVASE® had dissipated, but while heparin therapy was continuing.

As fibrin is lysed during ACTIVASE® therapy, bleeding from recent puncture sites may occur. Therefore, thrombolytic therapy requires careful attention to all potential bleeding sites (including sites of catheter insertion, arterial and venous puncture, cutdown and needle puncture).

Intramuscular injections and nonessential handling of the patient should be avoided during treatment with ACTIVASE®. Venipunctures should be performed carefully and only as required.

Should an arterial puncture be necessary during an infusion of ACTIVASE®, it is preferable to use an upper extremity vessel accessible to manual compression. Pressure should be applied for at least 30 minutes, a pressure dressing applied and the puncture site checked frequently for evidence of bleeding.

Should serious bleeding (not controllable by local pressure) occur, the infusion of ACTIVASE® and any concomitant heparin should be terminated immediately.

Each patient being considered for therapy with ACTIVASE® should be carefully evaluated and anticipated benefits weighed against potential risks associated with therapy.

In the following conditions, the risks of ACTIVASE® therapy may be increased and should be weighed against the anticipated benefits: • Recent (within 10 days) major surgery, e.g., coronary artery bypass graft, obstetrical delivery, organ biopsy, previous puncture of noncompressible vessels • Cerebrovascular disease • Recent (within 10 days) gastrointestinal or genitourinary bleeding • Recent (within 10 days) trauma • Hypertension: systolic BP≥180 mm Hg and/or diastolic BP≥110 mm Hg • High likelihood of left heart thrombus, e.g., mitral stenosis with atrial fibrillation • Acute pericarditis • Subacute bacterial endocarditis • Hemostatic defects including those secondary to severe hepatic or renal disease • Significant liver dysfunction • Pregnancy • Diabetic hemorrhagic retinopathy, or other hemorrhagic ophthalmic conditions • Septic thrombophlebitis or occluded AV cannula at seriously infected site • Advanced age, i.e., over 75 years old • Patients currently receiving oral anticoagulants • Any other condition in which bleeding constitutes a significant hazard or would be particularly difficult to manage because of its location.

Arrhythmias Coronary thrombolysis may result in arrhythmias associated with reperfusion. These arrhythmias are not different from those often seen in the ordinary course of AMI and may be managed with standard antiarrhythmic measures. It is recommended that antiarrhythmic therapy for bradycardia and/or ventricular irritability be available when infusions of ACTIVASE® are administered.

Pulmonary Embolism It should be recognized that the treatment of pulmonary embolism with ACTIVASE®, Alteplase, has not been shown to constitute adequate clinical treatment of underlying deep vein thrombosis. Furthermore, the possible risk of reembolization due to the lysis of underlying deep venous thrombi should be considered.

PRECAUTIONS: General Standard management of myocardial infarction or pulmonary embolism should be implemented concomitantly with ACTIVASE® treatment. Noncompressible arterial puncture must be avoided. Arterial and venous punctures should be minimized. In the event of serious bleeding, ACTIVASE® and heparin should be discontinued immediately. Heparin effects can be reversed by protamine.

Readministration There is no experience with readministration of ACTIVASE®. If anaphylactoid reaction occurs, infusion should be discontinued immediately and appropriate therapy initiated.

Although sustained antibody formation in patients receiving one dose of ACTIVASE® has not been documented, readministration should be undertaken with caution.

Laboratory Tests During ACTIVASE® therapy, results of coagulation tests and/or measures of fibrinolytic activity may be unreliable unless specific precautions are taken to prevent *in vitro* artifacts. ACTIVASE® is an enzyme that when present in blood in pharmacologic concentrations remains active under *in vitro* conditions. This can lead to degradation of fibrinogen in blood samples removed for analysis. Collection of blood samples in the presence of aprotinin (150-200 units/mL) can to some extent mitigate this phenomenon.

Drug Interactions The interaction of ACTIVASE® with other cardioactive drugs has not been studied. In addition to bleeding associated with heparin and vitamin K antagonists, drugs that alter platelet function (such as acetylsalicylic acid, dipyridamole) may increase the risk of bleeding if administered prior to, during or after ACTIVASE® therapy.

Use of Anticoagulants Heparin has been administered concomitantly with and following infusions of ACTIVASE® to reduce the risk of rethrombosis. Because either heparin or ACTIVASE® alone may cause bleeding complications, careful monitoring for bleeding is advised, especially at arterial puncture sites.

Pregnancy (Category C) Animal reproduction studies have not been conducted with ACTIVASE®. It is also not known whether ACTIVASE® can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. ACTIVASE® should be given to a pregnant woman only if clearly needed.

Pediatric Use Safety and effectiveness of ACTIVASE® in children has not been established.

Carcinogenesis, Mutagenesis, Impairment of Fertility Long-term studies in animals have not been performed to evaluate the carcinogenic potential or the effect on fertility. Short-term studies, which evaluated tumorigenicity of ACTIVASE® and effect on tumor metastases in rodents, were negative.

Studies to determine mutagenicity (Ames test) and chromosomal aberration assays in human lymphocytes were negative at all concentrations tested. Cytotoxicity, as reflected by a decrease in mitotic index, was evidenced only after prolonged exposure and only at the highest concentrations tested.

Nursing Mothers It is not known whether ACTIVASE® is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when ACTIVASE® is administered to a nursing woman.

ADVERSE REACTIONS: Bleeding The most frequent adverse reaction associated with ACTIVASE® is bleeding. The type of bleeding associated with thrombolytic therapy can be divided into two broad categories: • Internal bleeding involving the gastrointestinal or genitourinary tract, or retroperitoneal or intracranial sites • Superficial or surface bleeding, observed mainly at invaded or disturbed sites (e.g., sites of venous cutdown, arterial puncture, recent surgical intervention).

The following incidence of significant internal bleeding (estimated as >250 cc blood loss) has been reported in studies in over 800 patients treated at all doses:

	Total Dose ≤ 100 mg	Total Dose > 100 mg
gastrointestinal	5%	5%
genitourinary	4%	4%
ecchymosis	1%	<1%
retroperitoneal	<1%	<1%
epistaxis	<1%	<1%
gingival	<1%	<1%

The incidence of intracranial bleeding in patients treated with ACTIVASE®, Alteplase, recombinant, is as follows:

Dose	Number of Patients	%
100 mg	3272	0.4
150 mg	1779	1.3
1-1.4 mg/kg	237	0.4

These data indicate that a dose of 150 mg of ACTIVASE® should not be used because it has been associated with an increase in intracranial bleeding.

Recent data indicate that the incidence of stroke in 6 randomized double-blind placebo controlled trials[1-7] is not signficantly different in the ACTIVASE® treated patients compared to those treated with placebo (37/3161, 1.2% versus 27/3092, 0.9%, respectively) (p = 0.26).

Should serious bleeding in a critical location (intracranial, gastrointestinal, retroperitoneal, pericardial) occur, ACTIVASE® therapy should be discontinued immediately, along with any concomitant therapy with heparin.

Fibrin, which is part of the hemostatic plug formed at needle puncture sites, will be lysed during ACTIVASE® therapy. Therefore, ACTIVASE® therapy requires careful attention to potential bleeding sites.

Allergic Reactions No serious or life-threatening allergic reactions have been reported. Other mild hypersensitivity reactions such as urticaria have been observed occasionally.

Other Adverse Reactions Other adverse reactions have been reported, principally nausea and/or vomiting, hypotension, and fever. These reactions are frequent sequelae of MI and may or may not be attributable to ACTIVASE® therapy.

DOSAGE AND ADMINISTRATION: ACTIVASE® is for intravenous administration only. **ACUTE MYOCARDIAL INFARCTION: Administer ACTIVASE® as soon as possible after the onset of symptoms.**

The recommended dose is 100 mg administered as 60 mg (34.8 million IU) in the first hour (of which 6 to 10 mg is administered as a bolus over the first 1-2 minutes), 20 mg (11.6 million IU) over the second hour, and 20 mg (11.6 million IU) over the third hour. For smaller patients (less than 65 kg), a dose of 1.25 mg/kg administered over 3 hours, as described above, may be used.[8]

Although the use of anticoagulants and antiplatelet drugs during and following administration of ACTIVASE® has not been shown to be of unequivocal benefit, heparin has been administered concomitantly for 24 hours or longer in more than 90% of patients. Aspirin and/or dipyridamole have been given either during and/or following heparin treatment.

PULMONARY EMBOLISM: The recommended dose is 100 mg administered by intravenous infusion over two hours. Heparin therapy should be instituted or reinstituted near the end of or immediately following the ACTIVASE® infusion when the partial thromboplastin time or thrombin time returns to twice normal or less.

A DOSE OF 150 MG OF ACTIVASE® SHOULD NOT BE USED BECAUSE IT HAS BEEN ASSOCIATED WITH AN INCREASE IN INTRACRANIAL BLEEDING.

Reconstitution and Dilution DO NOT USE IF VACUUM IS NOT PRESENT.

ACTIVASE® should be reconstituted by aseptically adding the appropriate volume of the accompanying Sterile Water for Injection, USP to the vial. It is important that ACTIVASE® be reconstituted only with Sterile Water for Injection, USP, without preservatives. Do not use Bacteriostatic Water for Injection, USP. The reconstituted preparation results in a colorless to pale yellow transparent solution containing ACTIVASE® 1.0 mg/mL at approximately pH 7.3. The osmolality of this solution is approximately 215 mOsm/kg.

Because ACTIVASE® contains no antibacterial preservatives, it should be reconstituted immediately before use. The solution may be used for intravenous administration within 8 hours following reconstitution when stored between 2-30°C. Before further dilution or administration, the product should be visually inspected for particulate matter and discoloration prior to administration whenever solution and container permit.

ACTIVASE® may be administered as reconstituted at 1.0 mg/mL. As an alternative, the reconstituted solution may be diluted further immediately before administration in an equal volume of 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP to yield a concentration of 0.5 mg/mL. Either polyvinyl chloride bags or glass bottles are acceptable. ACTIVASE® is stable for up to 8 hours in these solutions at room temperature. Exposure to light has no effect on the stability of these solutions. Excessive agitation during dilution should be avoided; mixing should be accomplished with gentle swirling and/or slow inversion. Do not use other infusion solutions, e.g., Sterile Water for Injection, USP or preservative-containing solutions for further dilution.

No other medication should be added to infusion solutions containing ACTIVASE®. Any unused infusion solution should be discarded.

HOW SUPPLIED: ACTIVASE® is supplied as a sterile, lyophilized powder in 20 mg and 50 mg vials containing vacuum, each packaged with diluent for reconstitution.

Storage Store lyophilized ACTIVASE® at controlled room temperature not to exceed 30°C (86°F), or under refrigeration (2-8°C/36-46°F). Protect the lyophilized material during extended storage from excessive exposure to light.

Do not use beyond the expiration date stamped on the vial.

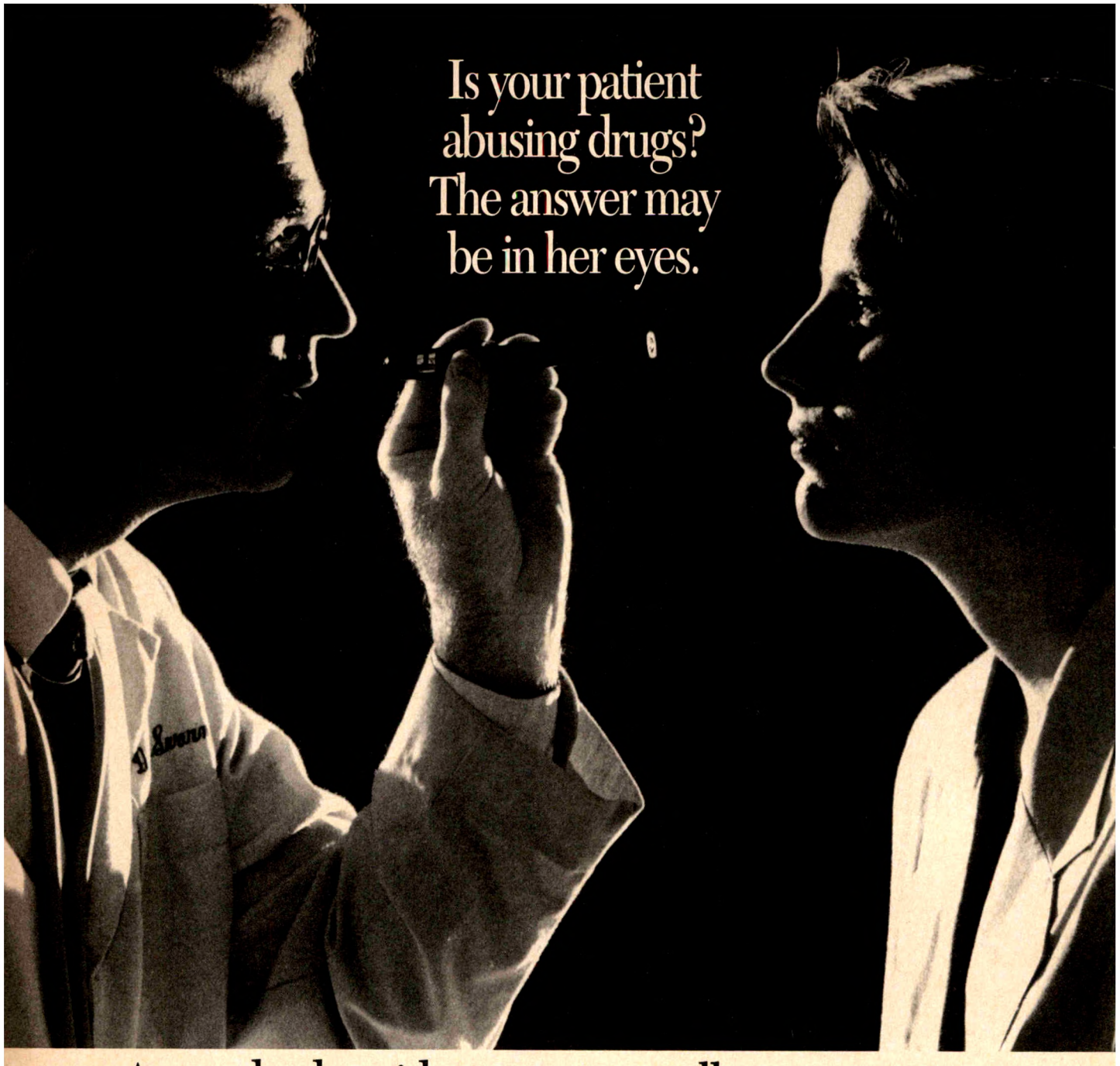
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Pupil size	Dilation; Constriction
Pupil reaction	Slow, sluggish, or absent response
Nystagmus	Failure to hold gaze; Jerkiness of movements
Convergence	Inability to track or hold the cross-eyed position
Corneal reflex	Decreased rate of blinking

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A Patency-Oriented Strategy for Early Management of Acute Myocardial Infarction Using Emergency Coronary Angiography and Selective Coronary Angioplasty

Jean-Michel Juliard, MD, P. Gabriel Steg, MD, Dominique Himbert, MD, Alain Cohen-Solal, MD, Marie-Claude Aumont, MD, and René Gourgon, MD

From June 1988 to March 1991, an unselected cohort of 150 consecutive patients with acute myocardial infarction (AMI) (<6 hours) was managed according to a strategy designed to ensure early patency of the infarct-related artery in the maximum number of patients. The following procedures were used: (1) intravenous thrombolysis, which was the usual treatment (n = 103), followed in 98 cases by emergency coronary angiography 90 minutes after the beginning of thrombolysis. This identified 31 thrombolysis failures (32%) and led to 19 rescue angioplasties (18 successes). All patients were then scheduled for predischarge angiography. (2) Direct angioplasty, which was performed in 40 patients because of contraindications to thrombolysis (n = 23), cardiogenic shock (n = 3), diagnostic doubt (n = 7) or "ideal" conditions for direct angioplasty (n = 7). Success (defined as Thrombolysis in Myocardial Infarction [TIMI] flow >1, with a residual stenosis <50% in the infarct-related artery) was achieved in 36 of 40 patients (90%). (3) The 7 remaining patients were given conventional medical treatment because of advanced age, contraindications to thrombolysis and angioplasty, or spontaneous reperfusion (confirmed by emergency angiography). In all, emergency angioplasty was performed in the acute phase in 39% of the 150 patients in this nonselected cohort. Despite the logistic burden involved, this strategy achieved a low in-hospital mortality rate (7 of 150 patients [4.7%]; 1.9% in those treated with thrombolysis) and a high infarct-related artery patency rate (both in the acute phase [88%] and at hospital discharge [93% of those with a predischarge angiogram]), whereas only a minimal number of patients (3.3%) had no benefit from early recanalization therapy. In conclusion, an aggressive revascularization strategy used during the acute phase in all patients with AMI (<6 hours) achieves high in-hospital patency and low in-hospital mortality.

(Am J Cardiol 1992;69:1383–1388)

From the Service de Cardiologie, Hôpital Bichat, Paris, France. This work was partially supported by the Fédération de Cardiologie, Paris, France. Manuscript received October 17, 1991; revised manuscript received January 27, 1992, and accepted January 28.

Address for reprints: Jean-Michel Juliard, MD, Service de Cardiologie, Hôpital Bichat, 46 Rue Henri Huchard, 75018 Paris, France.

It has been established that during developing acute myocardial infarction (AMI), early coronary recanalization improves survival and preserves left ventricular function.[1–3] Intravenous thrombolysis has rapidly become the preferred method. However, recanalization and patency studies have demonstrated that in approximately 30% of cases, the infarct-related artery remains occluded while the necrosis develops. Furthermore, even when thrombolysis successfully restores infarct-related artery patency, a reocclusion rate of 15 to 20% is frequent.[4] In addition, a significant number of patients cannot receive thrombolytic treatment, because of either absolute contraindications to thrombolysis or nondiagnostic electrocardiography. To limit the number of patients excluded from early recanalization therapy, because of either unsuccessful thrombolysis or contraindication to thrombolysis, we used a strategy consisting of either intravenous thrombolysis followed by emergency coronary angiography and, if necessary, rescue angioplasty or direct angioplasty for the triage and treatment of 150 consecutive patients with AMI presenting within 6 hours of the onset of pain. We report the in-hospital outcome for this nonselected cohort.

METHODS

From June 1988 to March 1991, 150 consecutive patients with AMI were admitted <6 hours after the onset of pain to our coronary care unit. AMI was defined as chest pain lasting >30 minutes and resistant to nitrates, with either typical electrocardiographic changes (ST-segment elevation >0.1 mV in 2 contiguous limb leads, or >0.2 mV in 2 contiguous chest leads) or giant T waves. The diagnosis of AMI was eventually confirmed in all patients by angiography, electrocardiographic changes and creatine phosphokinase elevation.

The following strategy was used: All patients underwent intravenous thrombolysis, except in cases of contraindication to thrombolysis, diagnostic doubt or cardiogenic shock. In these cases, emergency coronary angiography was performed, followed by direct angioplasty (if deemed suitable by the operator). Furthermore, several patients admitted in "ideal" conditions for direct angioplasty (i.e., immediate availability of catheterization laboratory and staff) and without contraindication to thrombolysis underwent direct angioplasty. Patients with contraindications to both thrombolysis and emergency angiography were given "conventional" medical treatment. All patients receiving thrombolysis underwent 90-minute coronary angiography to evaluate

the patency of the infarct-related artery (graded according to the Thrombolysis in Myocardial Infarction [TIMI] score).[5] If patency was graded 0 or 1 (i.e., unsuccessful thrombolysis), rescue angioplasty could be performed at the discretion of the operator. All patients were scheduled for a predischarge angiogram 5 to 10 days after admission. Several patients did not have this predischarge angiogram, because of in-hospital coronary artery bypass grafting or death, or because the infarct-related artery was judged to be unsuitable for revascularization on the initial angiogram. Emergency angiography was performed in cases of recurrent ischemia or cardiogenic shock. On admission, in the absence of contraindication, all patients were given 250 mg of aspirin (orally or intravenously) and underwent intravenous β-blockade with 5 mg of atenolol or metoprolol, followed by 250 mg of aspirin and 100 mg of atenolol or metoprolol daily. Intravenous heparin was used for ≥5 days, and intravenous nitrates (titrated according to blood pressure) were used for ≥24 hours.

Coronary angiography: Coronary angiography was performed after injection of 5,000 IU of heparin. Patients excluded from thrombolysis and eligible for direct angioplasty underwent angiography immediately on admission. Infarct-related artery patency was graded according to the TIMI score after ≥4 contrast injections. Thrombolysis success was defined as TIMI flow grade 2 or 3 in the infarct-related artery. The extent of coronary artery disease was also evaluated, and a vessel was judged to be significantly diseased if a stenosis >50% in diameter was present. Immediately after angiography, a continuous intravenous infusion of heparin (1,000 IU/hour) was begun and titrated every 4 hours, according to the activated partial thromboplastin time, until the latter was at least twice the control value.

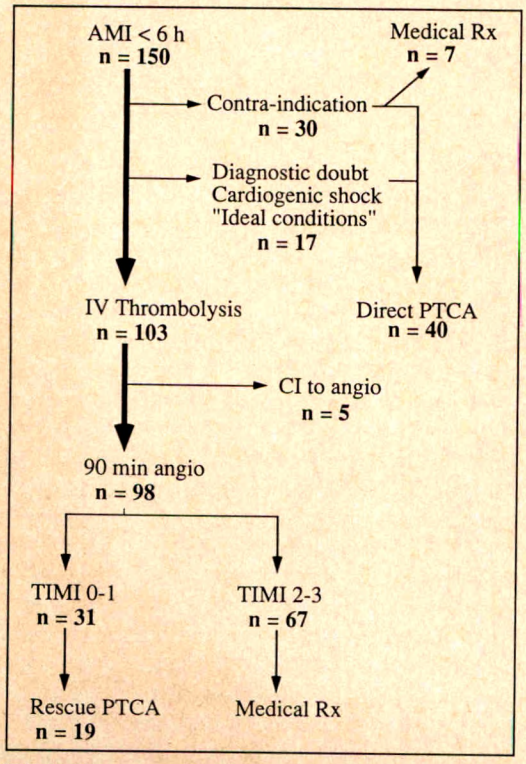


FIGURE 1. Management strategy for entire cohort. AMI = acute myocardial infarction; angio = coronary angiogram; CI = contraindication; IV = intravenous; PTCA = percutaneous transluminal coronary angioplasty; Rx = treatment, TIMI = Thrombolysis in Myocardial Infarction perfusion grade.

Coronary angioplasty: Percutaneous transluminal coronary angioplasty was performed by a femoral approach using a "monorail" balloon system, over a 0.014 inch ACS intermediate guidewire (Advanced Cardiovascular Systems, Temecula, California). Patients were given an intravenous bolus injection of 15,000 IU of heparin immediately before arterial insertion of the guidewire. Angioplasty success was defined as TIMI flow grade 2 or 3 in the infarct-related artery, with a residual stenosis <50%. Angioplasty of a noninfarct-related artery was not attempted during the acute phase.

Logistics: A 24-hour emergency catheterization system was instituted, with 3 trained physicians on call. Coronary care unit nurses underwent regular training in the catheterization laboratory and provided help when emergency catheterization was performed during the night shift (i.e., between 8:00 P.M. and 8:00 A.M. on weekdays) or on weekends.

RESULTS

The study population comprised 150 consecutive patients (119 men and 31 women, mean age 58 ± 11 years, range 34 to 91) with AMI developing for <6 hours, 59% of whom were admitted during the night shift or on weekends (Figure 1). During the same period, 60 patients were admitted >6 hours after the onset of pain. Infarct location was anterior in 80 cases, inferior in 69 and lateral in 1. All except 7 patients had transmural AMI (ST-segment elevation and new Q waves). The 7 patients with only T-wave changes were all managed with diagnostic coronary angiography followed by direct angioplasty. In this unselected cohort, 16% of patients were aged >70 years, 8% had a previous AMI, 37% had multivessel disease, and 3.3% were in cardiogenic shock on admission.

Intravenous thrombolysis (n = 103; Figures 2 and 3): Intravenous thrombolysis was instituted in 103 patients. The average interval between onset of chest pain and beginning of thrombolysis was 183 ± 78 minutes. The thrombolytic agents used were as follows: alteplase (total dose 1.5 mg/kg; n = 58) infused over 4 hours, at the rate of 1 mg/kg during the first hour (10% as a bolus), and 0.5 mg/kg as a maintenance infusion during the next 3 hours[6]; streptokinase (1.5 megaU; n = 13) infused over 1 hour; anistreplase (30 U bolus, n = 12); and a combination of alteplase and urokinase (n = 20) at the different dosages specified in the protocol of the Urokinase and Alteplase in Myocardial Infarction study.[7] All patients underwent emergency coronary angiography 90 minutes after the beginning of thrombolytic infusion, except for 5 with obvious contraindications to emergency coronary angiography due to problems of arterial femoral access (n = 3), agitation (n = 1) or morbid obesity (n = 1).

HEMORRHAGIC COMPLICATIONS: There was 1 fatal cerebral hemorrhage and 1 nonfatal cerebellar hemorrhage (confirmed by computed tomodensitometry) that led to the withholding of anticoagulant treatment. Two

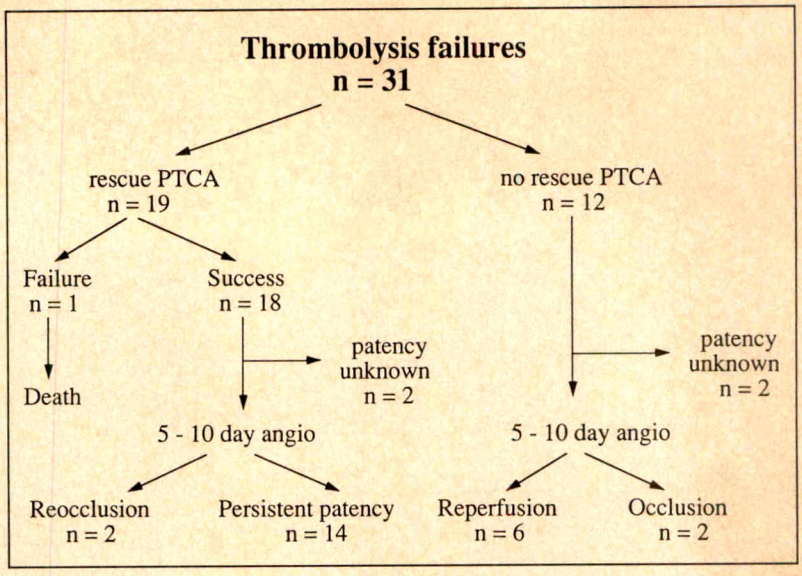


FIGURE 2. In-hospital outcome for patients with occluded infarct-related arteries 90 minutes after thrombolysis. Abbreviations as in Figure 1.

other patients had a decrease in hemoglobin levels (<8 g/100 ml) due to gastrointestinal hemorrhage and retroperitoneal hematoma, respectively, and both received blood transfusions.

EMERGENCY CORONARY ANGIOGRAPHY (N = 98): The infarct-related artery was identified in all cases. It was the left anterior descending artery in all 52 anterior wall AMIs, and the right coronary artery in 33 and left circumflex in 13 of 46 inferior wall AMIs. TIMI grade 2 or 3 patency of the infarct-related artery was seen in 67 patients, and grade 0 or 1 in 31 patients. The extent of coronary artery disease was graded as 1-, 2- or 3-vessel disease in 62, 20 and 16 of 98 patients (63, 20 and 17%), respectively. Before catheterization, 3 patients needed emergency cardiac pacing for symptomatic third-degree atrioventricular block on inferior wall AMIs. One patient presented with ventricular fibrillation during contrast injection, and sinus rhythm was immediately reestablished by cardioversion.

UNSUCCESSFUL THROMBOLYSIS (N = 31; FIGURE 2): TIMI grade 0 or 1 patency of the infarct-related artery was demonstrated in 31 of 98 cases (32%). There was 1 in-hospital death in this group (unsuccessful rescue angioplasty of left anterior descending artery in patient with cardiogenic shock). Nineteen of these 31 cases underwent immediate rescue angioplasty (10 in left anterior descending and 9 in right coronary artery), with 18 successes. Mean delay between onset of pain and reperfusion of the infarct-related artery was 331 ± 112 minutes. A subsequent coronary angiogram was performed before hospital discharge in 16 of these 18 patients, and disclosed silent reocclusion of the right coronary artery in 2.

Twelve patients did not undergo rescue angioplasty, because the infarct-related artery was judged unsuitable, or because of inclusion in the medical arm of the Randomized Evolution of Salvage Angioplasty with Combined Utilization of End Points (RESCUE) study (n = 2; see later). All patients had an uncomplicated hospital course and were discharged alive. Eight patients underwent predischarge coronary angiography that showed persistent occlusions in 2, and spontaneous reperfusions with significant residual stenosis in 6.

SUCCESSFUL THROMBOLYSIS (N = 67; FIGURE 3): TIMI grade 2 or 3 patency of the infarct-related artery was seen in 67 patients (68%). There was 1 in-hospital death in this group from cerebral hemorrhage. All patients were treated medically, regardless of the severity and angiographic appearance of the residual stenosis, and were scheduled for predischarge coronary angiography.

Before this scheduled coronary angiogram, 3 patients (4.5%) had early symptomatic reocclusion leading to emergency coronary angiography and angioplasty that was successful, with no increase in creatine phosphokinase levels. Two other patients underwent early coronary artery bypass grafting due to 3-vessel disease.

Sixty-one patients had a predischarge angiogram that showed silent reocclusion of the infarct-related artery in 2.

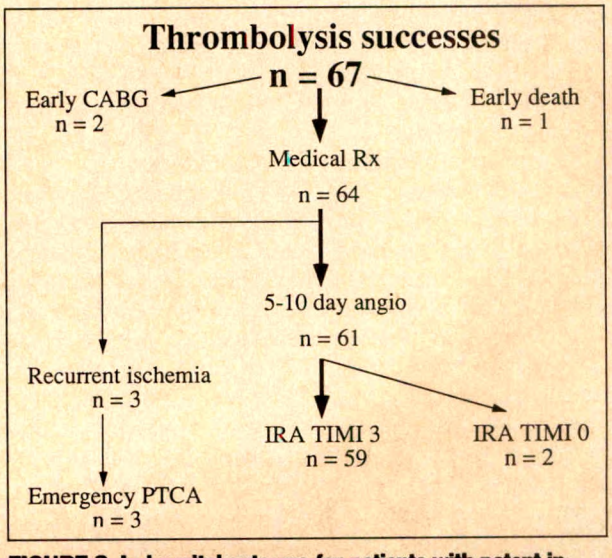


FIGURE 3. In-hospital outcome for patients with patent infarct-related arteries (IRA) 90 minutes after thrombolysis. CABG = coronary artery bypass grafting; other abbreviations as in Figure 1.

TABLE I Main In-Hospital Outcomes for the Cohort

	Intravenous Thrombolysis	Direct Angioplasty	Conventional Therapy	Total (%)
No. of pts.	103	40	7	150
Emergency angiogram	98	40	2	140/150 (93)
Emergency angioplasty	19	40	0	59/150 (39)
In-hospital death	2	4	1	7/150 (4.7)
Angiographically proven IRA patency (acute)	85	36	2	123/140 (88)
Angiographically proven IRA patency (discharge)	79	31	2	112/124 (93)

IRA = infarct-related artery.

Direct percutaneous transluminal coronary angioplasty (n = 40): Direct angioplasty was attempted in 40 patients (21 with anterior, 18 with inferior and 1 with lateral AMI). Indications for direct angioplasty were contraindications to thrombolysis in 23 cases, cardiogenic shock in 3, and nonfulfillment of the standard electrocardiographic criteria for thrombolysis[1] in 7. In the remaining 7 patients who had no contraindication to thrombolysis, ideal conditions for direct angioplasty led to elective performance of direct angioplasty.

The 23 patients with contraindications to thrombolysis had prolonged cardiopulmonary resuscitation (n = 5), recent surgery (n = 4), recent gastrointestinal hemorrhage or evolutive peptic ulcer (n = 7), or other causes (n = 7). Three patients were in cardiogenic shock (2 of whom had intraaortic balloon pump insertion). Emergency coronary angiography allowed identification of the infarct-related artery in all 40 patients: 21 anterior (20 left anterior descending artery and 1 left main trunk), 18 inferior (11 right coronary artery, 6 left circumflex and 1 saphenous vein graft) and 1 lateral (first diagonal branch) AMI. The extent of coronary artery disease was graded as 1-, 2- or 3-vessel disease in 25, 8 and 7 cases (62, 20 and 18%), respectively, with left main stenosis in 3.

The infarct-related artery was recanalized in 90% (36 of 40) of cases at 218 ± 100 minutes after the onset of pain and at 48 ± 31 minutes after admission. One patient died early of cardiogenic shock, despite a patent infarct-related artery and intraaortic balloon support, and 1 died of a noninfarct-related artery on the tenth day during angioplasty; an occlusion of the left main trunk was successfully recanalized, but a pericardial effusion complicated the procedure leading to emergency coronary bypass. Another patient in cardiogenic shock treated by emergency direct angioplasty and balloon pump counterpulsation underwent emergency coronary bypass, because of recurrent closure of the infarct-related artery. Two other patients underwent delayed elective coronary bypass. Of the 4 patients with unsuccessful direct angioplasty, 2 died, 1 underwent delayed elective coronary bypass, and 1 was treated medically. The latter patient underwent delayed angiography for late recurrent ischemia and had a patent infarct-related artery. One patient presented with symptomatic infarct-related artery reocclusion of the left anterior descending artery on the seventh day and was successfully redilated. Thirty patients had a predischarge coronary angiogram with no reocclusion.

"Conventional treatment": Seven patients were given conventional medical treatment with aspirin, heparin and β-blockade, because of advanced age and poor physiologic status in 3 cases (aged 91, 83 and 80 years, respectively), contraindications to both thrombolysis and emergency catheterization in 2, and strong suspicion of spontaneous reperfusion on admission in 2 (disappearance of chest pain, and normalization of ST-segment elevation). In the latter 2 cases, reperfusion of the infarct-related artery was immediately confirmed by an emergency angiogram performed to avoid overlooking ongoing AMI or incurring the hemorrhagic risks of an unnecessary thrombolysis. Further electrocardiographic and creatine kinase evolution confirmed the diagnosis of AMI.

In this group, 1 elderly patient in cardiogenic shock died. The 6 other patients survived, and 4 did not undergo cardiac catheterization. The 2 patients with spontaneous reperfusion underwent delayed angiography that showed a patent infarct-related artery.

Mortality (Table I): In-hospital mortality was 4.7% (7 of 150 patients). In the patients who underwent thrombolysis, mortality was 1.9% (2 of 103). When infarct-related artery patency was achieved during the acute phase, in-hospital mortality was 1.6% (2 of 123), but when patency was not achieved during this phase, mortality was 18.5% (5 of 27). Four of the 7 patients who died were in cardiogenic shock on admission. Conversely, of the 5 patients admitted in cardiogenic shock, 4 died.

Patency (Table I): Proven angiographic patency was achieved in 123 of 140 patients during the acute phase (88%) through spontaneous reperfusion, thrombolysis or angioplasty, or a combination. Emergency angioplasty (rescue or direct) was performed during the acute phase in 59 of 150 patients (39%).

Of the 124 patients who had a predischarge angiogram 5 to 10 days after admission, 116 had a patent infarct-related artery (93%). Infarct-related artery patency was not identified in 23 patients (16 who did not undergo a predischarge angiogram, and 7 who underwent coronary bypass), but these 116 patients represent ≥81% of those discharged alive, and 77% of the entire cohort (116 of 150).

DISCUSSION

In our cohort of 150 consecutive patients admitted with AMI <6 hours after the onset of pain, 140 (93%) underwent emergency coronary angiography and 59 (39%) emergency angioplasty (19 rescue and 40 direct). Only 7 patients had neither thrombolysis nor angioplasty during the acute phase, 2 of whom had proven acute reperfusion of the infarct-related artery. Therefore, in this management scheme, only 5 of 150 patients (3.3%) did not undergo an attempt at recanalization of

the infarct-related artery. This management strategy achieved a high infarct-related artery patency rate in both the acute phase (88%) and at hospital discharge (93% of those who underwent a predischarge angiogram; ≥81% of survivors), with low in-hospital mortality (4.7% for the entire cohort, and 1.9% for those treated with thrombolysis).

Benefit of achieving infarct-related artery patency: Early patency of the infarct-related artery reduces both the size of the myocardial infarct[8,9] and the mortality.[1-3,10-13] It is a prognostic factor independent of infarct size, and reopening the vessel beyond the time window for myocardial salvage can still result in improved prognosis.[14-16] Finally, in-hospital patency of the infarct-related artery has been shown to be a powerful prognostic indicator of long-term survival.[17] Therefore, establishment of early and sustained infarct vessel patency appears to be an important goal in the treatment of AMI,[16] and our strategy was designed to achieve the greatest possible infarct-related artery patency both in the acute phase and at hospital discharge. There is concern that patency achieved during the acute phase through angioplasty may not be as sustained as that achieved through thrombolysis, because of the high rate of reocclusion (up to 21% after rescue angioplasty).[18,19] However, this was not the case in our cohort, in which there were only 3 reocclusions (5.5%) of 54 successful emergency angioplasties compared with 5 reocclusions (7.4%) of 67 successful thrombolyses. This low rate of reocclusion after angioplasty was observed despite the fact that during the acute phase, angioplasty was aimed at restoring flow in the infarct-related artery with a residual stenosis <50% rather than optimizing the angiographic result.

Role of emergency coronary angiography: To achieve the present high patency rate, >93% of our patients underwent emergency angiography. This was necessary to identify the infarct-related artery, ascertain its patency status and set the stage for direct or rescue angioplasty. Early after thrombolysis, noninvasive criteria for the detection of reperfusion are imperfectly correlated to angiographic patency during the acute phase.[20] Thus, coronary angiography still constitutes the only accurate method of detecting unsuccessful thrombolysis. Furthermore, coronary angiography provides important ancillary information such as the extent of coronary artery disease, and identification of left main disease. Early availability of these data affects prognosis and patient management.

Role of rescue angioplasty: Unsuccessful thrombolysis is associated with high mortality.[11] Therefore, it has been suggested that in this patient subset, successful rescue angioplasty helps to reduce mortality.[21] However, because unsuccessful rescue angioplasty is associated with an extremely poor outcome,[18,19,22] its value is currently being assessed by an ongoing multicenter randomized trial (RESCUE study).

After successful thrombolysis, because of the risk of symptomatic reocclusion during the first days (10 to 15% in the literature, and 4.5% in our series),[4] our strategy of watchful waiting included the capability for urgent angioplasty in case of recurrent ischemia. This was designed to avoid wasting the benefit of successful thrombolysis, as repeat thrombolysis was contraindicated due to recent arterial access. In our study, 3 patients presented with acute recurrent ischemia that led to successful emergency angioplasty without reinfarction.

Direct angioplasty: Direct angioplasty[23-25] is the method of choice for the treatment of patients with an absolute contraindication to thrombolysis. It can also be used in patients with suspected AMI and nondiagnostic electrocardiograms on admission. Likewise, the chances of survival are much better in patients with cardiogenic shock treated by emergency angioplasty than in those given conventional medical treatment.[26,27] Together, these patient subsets (contraindication to thrombolysis, nondiagnostic electrocardiogram and cardiogenic shock) constitute a significant portion of the AMI population seen within 6 hours of the onset of pain (31.3% in our series). Therefore, it appears desirable that when possible, prehospital triage be organized to allow selective transfer of these patients to a center with immediate and permanent facilities for emergency angiography and angioplasty.

An unresolved issue is the role of direct angioplasty in patients who are candidates for intravenous thrombolysis. Until this issue is resolved by randomized trials, one can only point out that systematic direct angioplasty is a heavy burden on staff and resources. However, for selected patients admitted under ideal conditions (catheterization laboratory and staff available immediately) it appeared to be a safe and successful approach.

In-hospital mortality: The 4.7% mortality for our entire cohort compares favorably with that observed in all large-scale thrombolysis studies (Gruppa Italiano per lo Studio della Streptochinasi nell'Infarcto Miocardico[1]: 11%; and International Study of Infarct Survival-I[2]: 9%), even in carefully selected cohorts (TIMI phase II[28]: 5%; and APSAC International Mortality Study[29]: 6%). The fact that our cohort of 150 patients included 40 patients (26.7%) excluded from thrombolysis gives these results additional significance, because mortality in these patients is known to be increased (averaging 18.3% and reaching 24.9% in patients aged >76 years).[30] In our cohort of patients treated with thrombolysis, mortality was 1.9% (2 of 103).

The main limitation of this study is that it only provides in-hospital data on the outcome of this cohort. Whether our low early mortality and high rate of infarct-related artery patency will translate into improved long-term prognosis remains unknown, even though other studies suggest the long-term outcome for patients with patent infarct-related arteries after AMI is favorable.[17] Furthermore, the results obtained can only be compared with historic controls. Finally, despite the absence of selection bias, it is not certain that this cohort is representative of the "AMI patient mix" of other institutions. However, it does provide a realistic view of the use of an "aggressive" management strategy in an actual group of patients with AMI.

Acknowledgment: We are indebted to the catheterization laboratory team (Joëlle Cabanes, RN, Christine

Frelaud, RN, and Jacqueline Latulipe, RN) and coronary care unit nurses of Hôpital Bichat for assisting in the 24-hour catheterization effort.

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Hypotension: Symptomatic hypotension was rarely seen in uncomplicated hypertensive patients treated with ACCUPRIL but, as with other ACE inhibitors, it is a possible consequence of therapy in salt/volume depleted patients, such as those previously treated with diuretics or dietary salt restriction or who are on dialysis (see PRECAUTIONS, DRUG INTERACTIONS, and ADVERSE REACTIONS). In controlled studies, syncope was observed in 0.4% of patients (N = 3203); this incidence was similar to that observed for captopril (1%) and enalapril (0.8%).

In patients with concomitant congestive heart failure, with or without associated renal insufficiency, ACE inhibitor therapy may cause excessive hypotension, which may be associated with oliguria or azotemia and, rarely, with acute renal failure and death. In such patients, ACCUPRIL therapy should be started at the recommended dose under close medical supervision. These patients should be followed closely for the first 2 weeks of treatment and whenever the dosage of antihypertensive medication is increased (see DOSAGE AND ADMINISTRATION).

If symptomatic hypotension occurs, the patient should be placed in the supine position and, if necessary, normal saline may be administered intravenously. A transient hypotensive response is not a contraindication to further doses; however, lower doses of ACCUPRIL or reduced concomitant diuretic therapy should be considered.

Neutropenia/Agranulocytosis: Another ACE inhibitor, captopril, has been shown to cause agranulocytosis and bone marrow depression rarely in patients with uncomplicated hypertension, but more frequently in patients with renal impairment, especially if they also have a collagen vascular disease such as systemic lupus erythematosus or scleroderma. Agranulocytosis did occur during ACCUPRIL treatment in one patient with a history of neutropenia during previous captopril therapy. Available data from clinical trials of ACCUPRIL are insufficient to show that, in patients without prior reactions to other ACE inhibitors, ACCUPRIL does not cause agranulocytosis at similar rates. As with other ACE inhibitors, periodic monitoring of white blood cell counts in patients with collagen vascular disease and/or renal disease should be considered.

Fetal/Neonatal Morbidity and Mortality: ACE inhibitors can cause fetal and neonatal morbidity and death when administered to pregnant women. Several dozen cases have been reported in the world literature. When pregnancy is detected, ACE inhibitors should be discontinued as soon as possible.

The use of ACE inhibitors during the second and third trimesters of pregnancy has been associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death. Oligohydramnios has also been reported, presumably resulting from decreased fetal renal function; oligohydramnios in this setting has been associated with fetal limb contractures, craniofacial deformation, and hypoplastic lung development. Prematurity, intrauterine growth retardation, and patent ductus arteriosus have also been reported, although it is not clear whether these occurrences were due to the ACE inhibitor exposure.

These adverse effects do not appear to have resulted from intrauterine ACE inhibitor exposure that has been limited to the first trimester. Mothers whose embryos and fetuses are exposed to ACE inhibitors only during the first trimester should be so informed. Nonetheless, when patients become pregnant, physicians should make every effort to discontinue the use of ACCUPRIL as soon as possible.

Rarely (probably less often than once in every thousand pregnancies), no alternative to ACE inhibitors will be found. In these rare cases, the mothers should be apprised of the potential hazards to their fetuses, and serial ultrasound examinations should be performed to assess the intraamniotic environment.

If oligohydramnios is observed, ACCUPRIL should be discontinued unless it is considered life-saving for the mother. Contraction stress testing (CST), a non-stress test (NST), or biophysical profiling (BPP) may be appropriate, depending upon the week of pregnancy. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury.

Infants with histories of *in utero* exposure to ACE inhibitors should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion. Exchange transfusion or dialysis may be required as a means of reversing hypotension and/or substituting for disordered renal function. Removal of ACCUPRIL, which crosses the placenta, from the neonatal circulation is not significantly accelerated by these means.

No teratogenic effects of ACCUPRIL were seen in studies of pregnant rats and rabbits. On a mg/kg basis, the doses used were up to 180 times (in rats) and one time (in rabbits) the maximum recommended human dose.

PRECAUTIONS
General
Impaired renal function: As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients with severe heart failure whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with ACE inhibitors, including ACCUPRIL, may be associated with oliguria and/or progressive azotemia and rarely acute renal failure and/or death.

In clinical studies in hypertensive patients with unilateral or bilateral renal artery stenosis, increases in blood urea nitrogen and serum creatinine have been observed in some patients following ACE inhibitor therapy. These increases were almost always reversible upon discontinuation of the ACE inhibitor and/or diuretic therapy. In such patients, renal function should be monitored during the first few weeks of therapy.

Some hypertensive patients with no apparent preexisting renal vascular disease have developed increases in blood urea and serum creatinine, usually minor and transient, especially when ACCUPRIL has been given concomitantly with a diuretic. This is more likely to occur in patients with preexisting renal impairment. Dosage reduction and/or discontinuation of any diuretic and/or ACCUPRIL may be required.

Evaluation of hypertensive patients should always include assessment of renal function (see DOSAGE AND ADMINISTRATION).

Hyperkalemia and potassium-sparing diuretics: In clinical trials, hyperkalemia (serum potassium ≥5.8 mmol/L) occurred in approximately 2% of patients receiving ACCUPRIL. In most cases, elevated serum potassium levels were isolated values which resolved despite continued therapy. Less than 0.1% of patients discontinued therapy due to hyperkalemia. Risk factors for the development of hyperkalemia include renal insufficiency, diabetes mellitus, and the concomitant use of potassium-sparing diuretics, potassium supplements, and/or potassium-containing salt substitutes, which should be used cautiously, if at all, with ACCUPRIL (see PRECAUTIONS, Drug Interactions).

Cough: Cough has been reported with the use of ACE inhibitors. Characteristically, the cough is nonproductive, persistent, and resolves after discontinuation of therapy. ACE inhibitor-induced cough should be considered as part of the differential diagnosis of cough.

Surgery/anesthesia: In patients undergoing major surgery or during anesthesia with agents that produce hypotension, ACCUPRIL will block angiotensin II formation secondary to compensatory renin release. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by volume expansion.

Information for Patients
Pregnancy: Female patients of childbearing age should be told about the consequences of second- and third-trimester exposure to ACE inhibitors, and they should also be told that these consequences do not appear to have resulted from intrauterine ACE-inhibitor exposure that has been limited to the first trimester. These patients should be asked to report pregnancies to their physicians as soon as possible.

Angioedema: Angioedema, including laryngeal edema, can occur with treatment with ACE inhibitors, especially following the first dose. Patients should be so advised and told to report immediately any signs or symptoms suggesting angioedema (swelling of face, extremities, eyes, lips, tongue, difficulty in swallowing or breathing) and to stop taking the drug until they have consulted with their physician (see WARNINGS).

Symptomatic hypotension: Patients should be cautioned that lightheadedness can occur, especially during the first few days of ACCUPRIL therapy, and that it should be reported to a physician. If actual syncope occurs, patients should be told to not take the drug until they have consulted with their physician (see WARNINGS).

All patients should be cautioned that inadequate fluid intake or excessive perspiration, diarrhea, or vomiting can lead to an excessive fall in blood pressure because of reduction in fluid volume, with the same consequences of lightheadedness and possible syncope.

Patients planning to undergo any surgery and/or anesthesia should be told to inform their physician that they are taking an ACE inhibitor.

Hyperkalemia: Patients should be told not to use potassium supplements or salt substitutes containing potassium without consulting their physician (see PRECAUTIONS).

Neutropenia: Patients should be told to report promptly any indication of infection (eg, sore throat, fever) which could be a sign of neutropenia.

NOTE: As with many other drugs, certain advice to patients being treated with ACCUPRIL is warranted. This information is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects.

Drug Interactions
Concomitant diuretic therapy: As with other ACE inhibitors, patients on diuretics, especially those on recently instituted diuretic therapy, may occasionally experience an excessive reduction of blood pressure after initiation of therapy with ACCUPRIL. The possibility of hypotensive effects with ACCUPRIL may be minimized by either discontinuing the diuretic or cautiously increasing salt intake prior to initiation of treatment with ACCUPRIL. If it is not possible to discontinue the diuretic, the starting dose of quinapril should be reduced (see DOSAGE AND ADMINISTRATION).

Agents increasing serum potassium: Quinapril can attenuate potassium loss caused by thiazide diuretics and increase serum potassium when used alone. If concomitant therapy of ACCUPRIL with potassium-sparing diuretics (eg, spironolactone, triamterene, or amiloride), potassium supplements, or potassium-containing salt substitutes is indicated, they should be used with caution along with appropriate monitoring of serum potassium (see PRECAUTIONS).

Tetracycline and other drugs that interact with magnesium: Simultaneous administration of tetracycline with ACCUPRIL reduced the absorption of tetracycline by approximately 28% to 37%, possibly due to the high magnesium content in ACCUPRIL tablets. This interaction should be considered if coprescribing ACCUPRIL and tetracycline or other drugs that interact with magnesium.

Lithium: Increased serum lithium levels and symptoms of lithium toxicity have been reported in patients receiving concomitant lithium and ACE inhibitor therapy. These drugs should be co-administered with caution, and frequent monitoring of serum lithium levels is recommended. If a diuretic is also used, it may increase the risk of lithium toxicity.

Other agents: Drug interaction studies of ACCUPRIL with other agents showed:
- Multiple dose therapy with propranolol or cimetidine has no effect on the pharmacokinetics of single doses of ACCUPRIL.
- The anticoagulant effect of a single dose of warfarin (measured by prothrombin time) was not significantly changed by quinapril coadministration twice-daily.
- ACCUPRIL treatment did not affect the pharmacokinetics of digoxin.
- No pharmacokinetic interaction was observed when single doses of ACCUPRIL and hydrochlorothiazide were administered concomitantly.

Carcinogenesis, Mutagenesis, Impairment of Fertility
Quinapril hydrochloride was not carcinogenic in mice or rats when given in doses up to 75 or 100 mg/kg/day (50 to 60 times the maximum human daily dose, respectively, on a mg/kg basis and 3.8 to 10 times the maximum human daily dose when based on a mg/m^2 basis) for 104 weeks. Female rats given the highest dose level had an increased incidence of mesenteric lymph node hemangiomas and skin/subcutaneous lipomas. Neither quinapril nor quinaprilat were mutagenic in the Ames bacterial assay with or without metabolic activation. Quinapril was also negative in the following genetic toxicology studies: *in vitro* mammalian cell point mutation, sister chromatid exchange in cultured mammalian cells, micronucleus test with mice, *in vitro chromosome* aberration with V79 cultured lung cells, and in an *in vivo* cytogenetic study with rat bone marrow. There were no adverse effects on fertility or reproduction in rats at doses up to 100 mg/kg/day (60 and 10 times the maximum daily human dose when based on mg/kg and mg/m^2, respectively).

Pregnancy
Pregnancy Categories C (first trimester) and D (second and third trimesters): See WARNINGS, Fetal/Neonatal Morbidity and Mortality

Nursing Mothers
It is not known if quinapril or its metabolites are secreted in human milk. Quinapril is secreted to a limited extent, however, in milk of lactating rats (5% or less of the plasma drug concentration was found in rat milk). Because many drugs are secreted in human milk, caution should be exercised when ACCUPRIL is given to a nursing mother.

Geriatric Use
Elderly patients exhibited increased area under the plasma concentration time curve (AUC) and peak levels for quinaprilat compared to values observed in younger patients; this appeared to relate to decreased renal function rather than to age itself. In controlled and uncontrolled studies of ACCUPRIL where 918 (21%) patients were 65 years and older, no overall differences in effectiveness or safety were observed between older and younger patients. However, greater sensitivity of some older individual patients cannot be ruled out.

Pediatric Use
The safety and effectiveness of ACCUPRIL in children have not been established.

ADVERSE REACTIONS
ACCUPRIL has been evaluated for safety in 4960 subjects and patients. Of these, 3203 patients, including 655 elderly patients, participated in controlled clinical trials. ACCUPRIL has been evaluated for long-term safety in over 1400 patients treated for 1 year or more.

Adverse experiences were usually mild and transient.

Discontinuation of therapy because of adverse events was required in 4.7% of patients treated with ACCUPRIL in placebo-controlled hypertension trials.

Adverse experiences probably or possibly related to therapy or of unknown relationship to therapy occurring in 1% or more of the 1563 patients in placebo-controlled hypertension trials who were treated with ACCUPRIL are shown below.

Adverse Events in Placebo-Controlled Trials

	ACCUPRIL (N = 1563) Incidence (Discontinuance)	Placebo (N = 579) Incidence (Discontinuance)
Headache	5.6 (0.7)	10.9 (0.7)
Dizziness	3.9 (0.8)	2.6 (0.2)
Fatigue	2.6 (0.3)	1.0
Coughing	2.0 (0.5)	0.0
Nausea/Vomiting	1.4 (0.3)	1.9 (0.2)
Abdominal Pain	1.0 (0.2)	0.7

See PRECAUTIONS, Cough.

Clinical adverse experiences probably or possibly related, or of uncertain relationship to therapy, occurring in 0.5% to 1.0% (except as noted) of the patients treated with ACCUPRIL (with or without concomitant diuretic) in controlled or uncontrolled trials (N = 4397) and less frequent, clinically significant events seen in clinical trials or post-marketing experience (the rarer events are in italics) include (listed by body system):

General: back pain, malaise

Cardiovascular: palpitation, vasodilation, tachycardia, *heart failure, hyperkalemia, myocardial infarction, cerebrovascular accident, hypertensive crisis, angina pectoris, orthostatic hypotension, cardiac rhythm disturbances*

Gastrointestinal: dry mouth or throat, constipation, *gastrointestinal hemorrhage, pancreatitis, abnormal liver function tests*

Nervous/Psychiatric: somnolence, vertigo, syncope, *nervousness, depression*

Integumentary: increased sweating, pruritus, *exfoliative dermatitis, photosensitivity reaction*

Urogenital: *acute renal failure*

Other: amblyopia, pharyngitis, sinusitis, bronchitis, *agranulocytosis, thrombocytopenia*

Fetal/Neonatal Morbidity and Mortality
See WARNINGS, Fetal/Neonatal Morbidity and Mortality.

Angioedema: angioedema has been reported in patients receiving ACCUPRIL (0.1%). Angioedema associated with laryngeal edema may be fatal. If angioedema of the face, extremities, lips, tongue, glottis, and/or larynx occurs, treatment with ACCUPRIL should be discontinued and appropriate therapy instituted immediately. (See WARNINGS.)

Clinical Laboratory Test Findings
Hematology: (See WARNINGS)

Hyperkalemia: (See PRECAUTIONS)

Creatinine and blood urea nitrogen: Increases (↑1.25 times the upper limit of normal) in serum creatinine and blood urea nitrogen were observed in 2% and 2%, respectively, of patients treated with ACCUPRIL alone. Increases are more likely to occur in patients receiving concomitant diuretic therapy than in those on ACCUPRIL alone. These increases often remit on continued therapy.

*In some patients, the antihypertensive effect may diminish toward the end of the once-daily dosing interval. In such patients, an increase in dosage or twice-daily administration may be warranted.

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Safety of Combined Intravenous Beta-Adrenergic Blockade (Atenolol or Metoprolol) and Thrombolytic Therapy in Acute Myocardial Infarction

Belinda K. W. Green, FCP(SA), Gary D. Gordon, FCP(SA), Adrian R. Horak, FCP(SA), Robert N. Scott Millar, FCP(SA), and Patrick J. Commerford, FCP(SA)

One hundred thirty-one patients presenting with acute myocardial infarction (AMI) a mean of 3 hours after the onset of symptoms were treated with oral aspirin and intravenous thrombolytic therapy followed by heparin. One hundred eleven patients (85%) also received intravenous followed by oral β blockers. Twenty-one patients (19%) discontinued the β blocker because of complications. Five (4.5%) required the addition of diuretic drugs or converting enzyme inhibitors. Six patients (5%) discontinued the β blocker after complete mechanical revascularization, and 1 patient was noncompliant. Long-term treatment continued in 90 patients (69%) over a 2-year follow-up period (average 13 months). There were 3 infarct extensions and 3 reinfarctions (5%). Overall mortality at 2 years was 10%. Intravenous β blockers are well tolerated in most patients treated with thrombolytic agents, aspirin and heparin. They may further improve the survival benefit of chronic β blocker therapy in the period after AMI.

(Am J Cardiol 1992;69:1389–1392)

Thrombolytic therapy has been shown to reduce morbidity and mortality in patients with acute myocardial infarction (AMI). Adjunctive therapy with aspirin and heparin also improves prognosis (survival).[1–3] Intravenous β blockers given early in the course of AMI, without concurrent thrombolytic therapy, reduce early mortality. The mechanism is unclear but they reduce infarct size, confer electrical stability on ischemic myocardium, and possibly reduce the incidence of early cardiac rupture by reducing the rate and force of ventricular contraction.[4,5] Continued oral administration also has a substantial effect on late mortality.[6–8] Reinfarction and recurrent ischemic events are reduced in patients treated with tissue-type plasminogen activator and intravenous β blockers.[9] Despite the proven benefits, clinicians remain concerned about the use of intravenous β blockers in the early stages of AMI. We evaluated the safety of a policy of intravenous β-adrenergic blockade in 131 consecutive patients treated with a thrombolytic agent early (within 6 hours) after onset of symptoms of AMI.

Patients: All patients aged <75 years with a diagnosis of AMI seen within 6 hours of the onset of pain and treated with an intravenous thrombolytic agent were eligible for intravenous β-adrenergic blockade.

Contraindications to intravenous β blockers were (1) a history of asthma or bronchospasm, (2) current use of oral β blockers, (3) significant conduction disturbances, (4) systemic hypotension with a systolic blood pressure <90 mm Hg, and (5) clinical left ventricular failure or a history of heart failure under treatment.

METHODS

All patients received 150 mg of oral aspirin and a thrombolytic agent. Approximately 15 minutes after the completion of the infusion of the thrombolytic agent, either 15 mg of metoprolol or 5 mg of atenolol were given intravenously over a 5-minute period with close observation of vital signs. Oral atenolol, 50 mg twice daily, was begun 3 hours later and continued until hospital discharge, and thereafter at the discretion of the attending cardiologist. All patients received an intravenous infusion of 25,000 U of heparin over 24 hours, starting 6 hours after thrombolytic therapy. Coronary angiography was performed routinely at 24 to 72 hours or earlier if indicated. Patients underwent 70% submax-

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TABLE I Contraindications to Beta-Adrenergic Blockade

Contraindications	No. of Pts.
Left ventricular failure	5
Conduction disturbances	5
Extreme sinus bradycardia (2)	
First-degree heart block (1)	
Complete heart block (2)	5
Cardiogenic shock	4
Bronchospasm/asthma	2
Cardiomyopathy	1
Previous oral β blockade	2
Unknown	1
Total	20 (15%)

TABLE II Overall Discontinuation

Reason for Stopping	Number of Patients			
	First 24 Hours	Day 1 Dis.	After Dis.	Total
Left ventricular failure	7	6	4	17
Conduction disturbances*	2	—	—	2
Cardiogenic shock	1	—	—	1
Bronchospasm	1	—	—	1
After mechanical revascularization	—	2	4	6
Noncompliance	—	—	1	1
Total				27

*One patient with complete atrioventricular block; one patient with first-degree atrioventricular block and sinus bradycardia.
Dis. = discharge.

imal effort stress testing either before discharge or 90% effort stress testing at 1 month follow-up. Mechanical revascularization, either coronary angioplasty or coronary bypass grafting, was offered to all patients with mainstem stenosis or 3-vessel coronary disease and impaired left ventricular function, and those with spontaneous or inducible ischemia.

AMI was confirmed by serial enzyme estimations in all but 2 patients.

RESULTS

Beta-adrenergic blockade: One hundred thirty-one patients (104 men) were treated with thrombolytic agents, 33 with anistreplase (30 U), 4 with tissue-type plasminogen activator (100 mg), and 94 with streptokinase (1.5 million units). The average age was 52.9 (± 9.6) years and the average time from symptom onset to treatment was 3 (± 1.5) hours. There were 72 anterior and 59 inferior infarcts. One hundred eleven patients (85%) received intravenous β blockers. The reasons for withholding β blockers are listed in Table I.

Left ventricular failure (5 patients) and conduction disturbances (5 patients) were the most common reasons for withholding the drug. The latter only occurred in those with inferior infarction. Cardiogenic shock was present in 4 patients; all died shortly after admission.

Of the original 111 patients given β blockers, 11 (10%) had discontinued the drug in the following 24-hour period. A further 6 (5%) discontinued the β blocker before discharge because of persistent left ventricular failure. In a further 5 patients (4.5%), additional therapy in the form of diuretic drugs or angiotensin-converting enzyme inhibitors enabled continuation of the β blocker.

During the follow-up period (mean 13.3 ± 6 months) 4 patients (4%) discontinued the β blocker because of persistent heart failure, and 6 (5%) after complete mechanical revascularization. One patient was noncompliant (Table II).

Infarct extension: The diagnosis of infarct extension was based on clinical symptoms, new electrocardiographic changes and a diagnostic enzyme increase after the initial 24-hour period. Three patients (2%) had evidence of infarct extension; one occurred after gastrointestinal bleeding that caused profound hypotension.

Reinfarction: There were 3 reinfarctions in the follow-up period. They occurred at 2 weeks, and 1 and 13 months after the initial episode. Two were in the same site as the initial infarction and 1 was remote. None had evidence of inducible ischemia.

Mortality: Four patients died from cardiogenic shock in the initial 24-hour period. None of these patients received intravenous β blockers. Two other patients died suddenly during hospital admission and another during coronary bypass grafting performed urgently for symptomatic mainstem stenosis. The early (in-hospital) mortality rate was thus 5%.

During follow-up, 1 patient died after coronary artery bypass grafting and there were 5 sudden out-of-hospital deaths. The 1-month mortality was 7% and at 2 years (± 13.3 months) the overall mortality was 10% (Figure 1).

DISCUSSION

This study was designed to assess the feasibility and safety of treating as many patients as possible with intravenous β-adrenergic blockade after thrombolytic therapy.

Clinical trials performed in the 1970s and early 1980s showed that intravenous β blockers given early in AMI reduced mortality by 30% at 24 hours and by 15% at 7 days.[4] Chronic oral administration of β blockers after infarction reduces mortality by 20%.[10]

Subgroup analysis of the causes of early mortality in a major study of intravenous β blockade indicates that many of the patients who died suddenly, died from cardiac rupture or from electromechanical dissociation, the usual clinical presentation of cardiac rupture.[4,5] The major impact on mortality in that study occurred within the first 24 hours, and β blockers could have reduced the incidence of acute cardiac rupture. Despite the evidence in favor of β-adrenergic blockade in AMI,[11–13] reports of its use in patients receiving thrombolytic therapy are limited. Additionally, nonfatal reinfarction and recurrent ischemic events were reduced in 1 report.[9]

A meta-analysis[10] of randomized β-blocker trials found that most series reported an increased evidence of sinus bradycardia and hypotension. Few reported a need

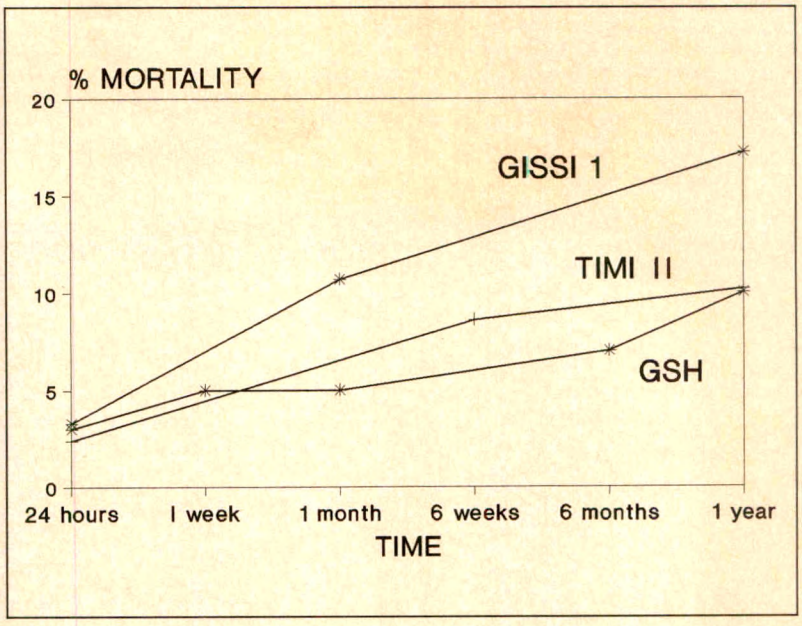


FIGURE 1. Cumulative mortality (cardiac deaths). GISSI = Gruppo Italiano Per Lo Studio Della Streptochinasi Nell' Infarto Miocardico[1]; GSH = Groote Schuur Hospital; TIMI II = Thrombolysis in Acute Myocardial Infarction[9]; X axis = time from admission; Y axis = percent mortality.

for atropine, and no excess of atrioventricular block was noted. In our study, 2 patients developed atrioventricular node conduction problems, both of whom had acute inferior infarctions, a condition well known to predispose to conduction problems. One patient developed first-degree heart block and one patient developed complete heart block; neither patient required further treatment.

Beta blockers were discontinued in 7 of our patients (6%) during the first 24 hours because of left ventricular failure unresponsive to the addition of diuretic drugs or converting enzyme inhibitors. A further 6 (5%) discontinued β-blocker treatment because of persistent left ventricular failure during their hospital admission, and an additional 4 (4%) because of left ventricular failure during the follow-up period. In all, 17 patients (15%) receiving intravenous and then oral β blockers discontinued the drug because of left ventricular failure. In our study, only 1 patient developed cardiogenic shock after administration of the β blocker. He was a 50-year-old man with a previous inferior myocardial infarction who presented with a large anterior myocardial infarct. He developed cardiogenic shock within 15 minutes of receiving the drug but survived with inotropic support. Angiography revealed a global, very poorly contracting left ventricle with moderate mitral regurgitation and quadruple vessel disease. He died 13 months later while awaiting heart transplantation.

In the Thrombolysis in Myocardial Infarction II-B[14] trial only 48.4% of patients were considered suitable for β-adrenergic blockade. In comparison, 111 of 131 of our patients (85%) were considered suitable for a therapy with β blockers. Three patients who discontinued their β-blocker therapy in the first 24 hours restarted therapy during the hospital admission; 4 other patients with contraindications to intravenous β blockers began oral therapy during their hospital stay (within 1 week). Therefore, of the 131 patients, 111 (85%) received intravenous and 90 (69%) received long-term oral β blockers.

With regard to reinfarction, infarct extension and recurrent ischemic events, the Thrombolysis in Myocardial Infarction II-B trial showed that there was a reduction in recurrent ischemic events at 6 days in the immediate versus delayed treatment groups (15.4 vs 21.2%, $p = 0.005$). In our group of patients, 17 (15%) had recurrent ischemic events in the first 6 days, which according to our protocol required mechanical revascularization.

The incidence of infarct extension and reinfarction at 42 days in the previously mentioned study was 7.3%; our long-term follow-up infarct extension/reinfarction rates are 5% (6 patients).

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RYTHMOL (propafenone HCl) is indicated for the treatment of documented ventricular arrhythmias, such as sustained ventricular tachycardia, that in the judgement of the physician, are life-threatening. Because of the proarrhythmic effects of RYTHMOL, its use should be reserved for patients in whom, in the opinion of the physician, the benefits of treatment outweigh the risks. The use of RYTHMOL is not recommended for use in patients with less severe ventricular arrhythmias, even if the patients are symptomatic. Use of RYTHMOL for the treatment of sustained ventricular tachycardia, like other antiarrhythmics, should be initiated in the hospital.

CONTRAINDICATIONS
RYTHMOL (propafenone HCl) is contraindicated in the presence of uncontrolled congestive heart failure, cardiogenic shock, sinoatrial, atrioventricular and intraventricular disorders of impulse generation and/or conduction (e.g., sick sinus node syndrome, atrioventricular block) in the absence of an artificial pacemaker, bradycardia, marked hypotension, bronchospastic disorders, manifest electrolyte imbalance, and known hypersensitivity to the drug.

WARNINGS:
Mortality: In the National Heart Lung and Blood Institute's Cardiac Arrhythmia Suppression Trial (CAST), a longterm, multicenter, randomized, double blind study in patients with asymptomatic non life threatening ventricular ectopy who had a myocardial infarction more than six days but less than two years previously and demonstrated mild to moderate left ventricular dysfunction, an excessive mortality or nonfatal cardiac arrest rate was seen in patients treated with encainide or flecainide (56/730) compared with that seen in patients assigned to carefully matched placebo treated groups (22/725). The average duration of treatment with encainide or flecainide in this study was ten months.The applicability of these results to other populations (e.g., those without recent myocardial infarction and to other antiarrhythmic drugs) is uncertain, but at present it is prudent (1) to consider any IC agent (especially one documented to provoke new serious arrhythmias) to have a similar risk and (2) to consider the risks of Class IC agents, coupled with the lack of any evidence of improved survival, generally unacceptable in patients without life threatening ventricular arrhythmias, even if the patients are experiencing unpleasant, but not life threatening, symptoms or signs.

Proarrhythmic Effects
RYTHMOL, like other antiarrhythmic agents, may cause new or worsened arrhythmias. Such proarrhythmic effects range from an increase in frequency of PVCs to the development of more severe ventricular tachycardia, ventricular fibrillation or torsade de pointes; i.e., tachycardia that is more sustained or more rapid which may lead to fatal consequences. It is therefore essential that each patient given RYTHMOL be evaluated electrocardiographically and clinically prior to, and during therapy to determine whether the response to RYTHMOL (propafenone HCl) supports continued treatment. Overall in clinical trials with propafenone, 4.7% of all patients had new or worsened ventricular arrhythmia possibly representing a proarrhythmic event (0.7% was an increase in PVCs; 4.0% a worsening, or new appearance, of VT or VF). Of the patients who had a worsening of VT (4%), 92% had a history of VT and/or VT/VF, 71% had coronary artery disease, and 68% had a prior myocardial infarction. The incidence of proarrhythmia in patients with less serious or benign arrhythmias, which include patients with an increase in frequency of PVCs, was 1.6%. Although most proarrhythmic events occurred during the first week of therapy, late events also were seen and the CAST study (see above) suggests that an increased risk is present throughout treatment.

Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema)
PATIENTS WITH BRONCHOSPASTIC DISEASE SHOULD IN GENERAL NOT RECEIVE PROPAFENONE or other agents with beta adrenergic blocking activity.

Congestive Heart Failure
During treatment with oral propafenone in patients with depressed baseline function (mean EF=33.5%), no significant decreases in ejection fraction were seen. In clinical trial experience, new or worsened CHF has been reported in 3.7% of patients; of those 0.9% were considered probably or definitely related to RYTHMOL. Of the patients with congestive heart failure probably related to propafenone, 80% had preexisting heart failure and 85% had coronary artery disease. CHF attributable to RYTHMOL developed rarely (<0.2%) in patients who had no previous history of CHF. As RYTHMOL exerts both beta blockade and a (dose related) negative inotropic effect on cardiac muscle, patients with congestive heart failure should be fully compensated before receiving RYTHMOL. If congestive heart failure worsens, RYTHMOL should be discontinued (unless congestive heart failure is due to the cardiac arrhythmia) and, if indicated, restarted at a lower dosage only after adequate cardiac compensation has been established.

Conduction Disturbances
RYTHMOL slows atrioventricular conduction and also causes first degree AV block. Average PR interval prolongation and increases in QRS duration are closely correlated with dosage increases and concomitant increases in propafenone plasma concentrations. The incidence of first degree, second degree, and third degree AV block observed in 2,127 patients was 2.5%, 0.6%, and 0.2%, respectively. Development of second or third degree AV block requires a reduction in dosage or discontinuation of RYTHMOL. Bundle branch block (1.2%) and intraventricular conduction delay (1.1%) have been reported in patients receiving propafenone. Bradycardia has also been reported (1.5%). Experience in patients with sick sinus node syndrome is limited and these patients should not be treated with propafenone.

Effects on Pacemaker Threshold
RYTHMOL may alter both pacing and sensing thresholds of artificial pacemakers. Pacemakers should be monitored and programmed accordingly during therapy.

Hematologic Disturbances
One case of agranulocytosis with fever and sepsis, probably related to use of propafenone, was seen in U.S. clinical trials. The agranulocytosis appeared after 8 weeks of therapy. Propafenone therapy was stopped and the white count had normalized by 14 days. The patient recovered. In the course of over 800,000 patient years of exposure during marketing outside the U.S. since 1978, seven additional cases have been reported. In one of these, concomitant captopril, a drug known to cause agranulocytosis, was used. Unexplained fever and/or decrease in white cell count, particularly during the first three months of therapy, warrant consideration of possible agranulocytosis/granulocytopenia. Patients should be instructed to promptly report the development of any signs of infection such as fever, sore throat, or chills.

PRECAUTIONS
Hepatic Dysfunction:
Propafenone is highly metabolized by the liver and should, therefore, be administered cautiously to patients with impaired hepatic function. The dose of propafenone given to patients with impaired hepatic function should be significantly reduced. Careful monitoring for excessive pharmacological effects (see OVERDOSAGE) should be carried out.

Renal Dysfunction:
A considerable percentage of propafenone metabolites (18.5%-38% of the dose/48 hours) are excreted in the urine. Until further data are available, RYTHMOL should be administered cautiously to patients with impaired renal function. These patients should be carefully monitored for signs of overdosage (see OVERDOSAGE).

Elevated ANA Titers:
Positive ANA titers have been reported in patients receiving propafenone. Patients who develop an abnormal ANA test should be carefully evaluated and, if persistent or worsening elevation of ANA titers is detected, consideration should be given to discontinuing therapy.

Impaired Spermatogenesis:
Reversible disorders of spermatogenesis have been demonstrated in monkeys, dogs and rabbits after high dose intravenous administration. Evaluation of the effects of short term propafenone administration on spermatogenesis in 11 normal subjects suggests that propafenone produced a reversible, short term drop (within normal range) in sperm count. Subsequent evaluations in 11 patients receiving propafenone chronically have suggested no effect of propafenone on sperm count.

Drug Interactions: Quinidine: Small doses of quinidine completely inhibit the hydroxylation metabolic pathway, making all patients, in effect, slow metabolizers. There is, as yet, too little information to recommend concomitant use of propafenone and quinidine. **Local Anesthetics:** Concomitant use of local anesthetics may increase the risks of central nervous system side effects. **Digitalis:** RYTHMOL produces dose related increases in serum digoxin levels ranging from about 35% at 450 mg/day to 85% at 900 mg/day propafenone without affecting digoxin renal clearance. Digoxin dosage should ordinarily be reduced when propafenone is started. **Beta-Antagonists:** Propafenone appears to inhibit the hydroxylation pathway for propranolol and metoprolol (just as quinidine inhibits propafenone metabolism). While the therapeutic range for beta-blockers is wide, a reduction in dosage may be necessary during concomitant administration with propafenone. **Warfarin:** In a study of eight healthy subjects receiving propafenone and warfarin concomitantly, mean steady-state warfarin plasma concentrations increased 39% with a corresponding increase in prothrombin times of approximately 25%. It is therefore recommended that prothrombin times be routinely monitored and the dose of warfarin be adjusted if necessary. **Cimetidine:** Concomitant administration of propafenone and cimetidine in 12 healthy subjects resulted in a 20% increase in steady-state plasma concentrations of propafenone with no detectable changes in electrocardiographic parameters beyond that measured on propafenone alone. **Other:** Limited experience with propafenone combined with calcium antagonists and diuretics has been reported without evidence of clinically significant adverse reactions.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Life time maximally tolerated oral dose studies in mice (up to 360 mg/kg/day) and rats (up to 270 mg/kg/day) provided no evidence of a carcinogenic potential for propafenone. RYTHMOL was not mutagenic when assayed for genotoxicity. **Pregnancy Teratogenic Effects:** Pregnancy Category C.: Propafenone has been shown to be embryotoxic in rabbits and rats when given in doses 10 and 40 times, respectively, the maximum recommended human dose. No teratogenic potential was apparent in either species. There are no adequate and well controlled studies in pregnant women. Propafenone should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. **Pregnancy Nonteratogenic Effects:** In a perinatal and postnatal study in rats, propafenone, at dose levels of 6 or more times the maximum recommended human dose, produced dose dependent increases in maternal and neonatal mortality, decreased maternal and pup body weight gain and reduced neonatal physiological development. **Labor and Delivery:** It is not known whether the use of propafenone during labor or delivery has immediate or delayed adverse effects on the fetus, or whether it prolongs the duration of labor or increases the need for forceps delivery or other obstetrical intervention. **Nursing Mothers:** It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from RYTHMOL, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: The safety and efficacy of RYTHMOL in children has not been established.

Geriatric Use: There do not appear to be any age-related differences in adverse reaction rates in the most commonly reported adverse reactions. Because of the possible increased risk of impaired hepatic or renal function in this age group, RYTHMOL should be used with caution. The effective dose may be lower in these patients.

ADVERSE REACTIONS
Adverse reactions associated with RYTHMOL (propafenone HCl) occur most frequently in the gastrointestinal, cardiovascular, and central nervous systems. About 20% of patients discontinued due to adverse reactions.
Adverse reactions reported for ≥1% of 2,127 patients who received propafenone in U.S. clinical trials are presented in the following list. Dizziness, Nausea and/or Vomiting, Unusual Taste, Constipation, Fatigue, Dyspnea, Proarrhythmia, Angina, Headache(s), Blurred Vision, CHF, Ventricular Tachycardia, Dyspepsia, Palpitations, Rash, First Degree AV Block, Diarrhea, Weakness, Dry Mouth, Syncope/Near Syncope, Increased QRS Duration, Chest Pain, Anorexia, Abdominal Pain/Cramps, Ataxia, Insomnia, Premature Ventricular Contraction(s), Bradycardia, Anxiety, Edema, Tremor(s), Diaphoresis, Bundle Branch Block, Drowsiness, Atrial Fibrillation, Flatulence, Hypotension, Intraventricular Conduction Delay, Joint(s) Pain.
In addition, the following adverse reactions were reported less frequently than 1% either in clinical trials or in marketing experience *(adverse events for marketing experience are given in italics)*. Causality and relationship to propafenone therapy can not necessarily be judged from these events. **Cardiovascular System**: Atrial flutter, AV dissociation, cardiac arrest, flushing, hot flashes, sick sinus syndrome, sinus pause or arrest, supraventricular tachycardia. **Nervous System:** Abnormal dreams, abnormal speech, abnormal vision, *apnea, coma,* confusion, depression, memory loss, numbness, paresthesias, psychosis/mania, seizures (0.3%), tinnitus, unusual smell sensation, vertigo. **Gastrointestinal:** A number of patients with liver abnormalities associated with propafenone therapy have been reported in foreign postmarketing experience. Some appeared due to hepatocellular injury, some were cholestatic and some showed a mixed picture. Some of these reports were simply discovered through clinical chemistries, others because of clinical symptoms. One case was rechallenged with a positive outcome. Cholestasis (0.1%), elevated liver enzymes (alkaline phosphatase, serum transaminases) (0.2%), gastroenteritis, hepatitis (0.03%) **Hematologic**: Agranulocytosis, anemia, bruising, granulocytopenia, *increased bleeding time,* leukopenia, purpura, thrombocytopenia. **Other**: Alopecia, eye irritation, *hyponatremia/inappropriate ADH secretion,* impotence, increased glucose, *kidney failure,* positive ANA (0.7%), *lupus erythematosis,* muscle cramps, muscle weakness, nephrotic syndrome, pain, pruritus.

OVERDOSAGE
The symptoms of overdosage, which are usually most severe within 3 hours of ingestion, may include hypotension, somnolence, bradycardia, intraatrial and intraventricular conduction disturbances, and rarely convulsions and high grade ventricular arrhythmias. Defibrillation as well as infusion of dopamine and isoproterenol have been effective in controlling rhythm and blood pressure. Convulsions have been alleviated with intravenous diazepam. General supportive measures such as mechanical respiratory assistance and external cardiac massage may be necessary.

RE-3Ry 4819-6/89/6-29-89

Printed in U.S.A.

Print No. 4819

Knoll Pharmaceuticals
A Unit of BASF K&F Corporation
Whippany, New Jersey 07981

BASF Group

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Recommended Dosage

Begin therapy with Rythmol 150 mg q8h (450 mg/day)

Increase to 225 mg q8h (incremental increases can be implemented after 3 or 4 days)(675 mg/day)

If necessary increase to 300 mg q8h (Maximum recommended dose 900 mg/day)

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R5025/ 4-91

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1. Data on file, Knoll Pharmaceuticals. 2. Adapted from Valero dePesce, E. V., et al: Oral Propafenone Efficacy in the Induction of Ventricular Tachycardia, *J. Electro,* 2 (3), 1988. 3. Dinh, H., Murphy, M.L., Baker, B.J., et al: Efficacy of propafenone compared with quinidine in chronic ventricular arrhythmias, *Am J Cardiol,* 55:1520, 1985. 4. Zoble, R. G., et al: Pharmacokinetic and pharmacodynamic evaluation of propafenone in patients with ventricular arrhythmia, *Clin Pharmacol and Ther,* 1989, 45:535-41.

Effectiveness and Safety of a Single Intravenous Bolus Injection of Tissue-Type Plasminogen Activator in Acute Myocardial Infarction

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The efficacy of multiple intravenous bolus injections of tissue-type plasminogen activator (t-PA) in inducing rapid coronary recanalization in patients with acute myocardial infarction was previously demonstrated. In this Bolus Dose-Escalation Study of Tissue-Type Plasminogen Activator (BEST), the efficacy of 3 different doses of a single rapid intravenous bolus injection of t-PA (duteplase, Wellcome Foundation, London) in inducing coronary patency (Thrombolysis In Myocardial Infarction perfusion grade 2 or 3) in 64 patients with acute myocardial infarction presenting <6 hours after onset of symptoms was investigated. At 60 minutes after administration of t-PA, the infarct-related coronary artery was patent in 9 of 17 patients (53%; 95% confidence interval [CI] 28 to 77%) after 0.3 MU/kg, in 14 of 23 (61%; 95% CI 39 to 80%) after 0.45 MU/kg and in 10 of 14 (71%; 95% CI 42 to 92%) after 0.6 MU/kg. At 90 minutes after t-PA, coronary patency was present in 9 of 17 cases (53%; 95% CI 28 to 77%) after 0.3 MU/kg, in 12 of 24 (50%; 95% CI 29 to 71%) after 0.45 MU/kg and in 10 of 13 (77%; 95% CI 46 to 95%) after 0.6 MU/kg. One patient in each dose group had a silent reoccluded infarct-related artery by 24 hours, and there were 2 clinical reinfarctions before discharge. No major bleeding events were observed. There were 5 hospital deaths, all unrelated to t-PA. A single intravenous bolus injection of 0.6 MU/kg of t-PA appears to be effective in inducing rapid coronary patency and to be safe in patients with acute myocardial infarction.

(Am J Cardiol 1992;69:1393–1398)

From the Bolus Dose-Escalation Study of Tissue-Type Plasminogen Activator (BEST) investigators (see Appendix for investigators, institutions and addresses). This study was supported in part by the British Heart Foundation, the Medical Research Council (Grant G7910332) and the Wellcome Foundation, London, United Kingdom. Dr. Andreotti is the recipient of British Heart Foundation project Grant 90/151. Dr. Haider is supported by a scholarship from the Ministry of Science and Technology, Government of Pakistan. Manuscript received December 17, 1991; revised manuscript received January 27, 1992, and accepted January 28.

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A single, rapidly administered, intravenous bolus injection of tissue-type plasminogen activator (t-PA) in patients with acute myocardial infarction may achieve earlier coronary thrombolysis than may conventional intravenous infusions as a result of the higher concentration of the drug attained in the blood. We previously demonstrated the effectiveness and advantages of multiple intravenous bolus administrations of t-PA, and observed a similar but possibly faster rate of acute coronary recanalization without an increased incidence of bleeding events or early reocclusion compared with that of a conventional intravenous infusion.[1] In that pilot study we discussed several potential advantages of bolus dosing over prolonged infusions of t-PA (i.e., ease of administration, rapid recanalization, reduction in the duration of acute myocardial ischemia and the systemic fibrinolytic state, and possibly fewer bleeding complications). In this Bolus Dose-Escalation Study of Tissue-Type Plasminogen Activator (BEST), we examined the efficacy and safety of a single intravenous bolus injection in achieving prompt coronary patency in patients with acute myocardial infarction. We also examined the effects of single bolus administration of t-PA on electrocardiographic resolution of ischemia and on fibrinogen consumption.

METHODS

Patients: From April 1989 to October 1990, 64 patients (50 men and 14 women, aged ≤75 years, mean 60, range 33 to 75) with continuous chest pain typical of acute myocardial ischemia of 0.5 to 6 hours duration were entered in the study at 4 different centers (see Appendix for participating institutions). All patients had electrocardiographic ST-segment elevation of ≥0.1 mV in 2 contiguous limb leads, or ≥0.2 mV in 2 contiguous chest leads, or ST-segment depression ≥0.2 mV in 2 contiguous anterior chest leads indicative of posterior infarction.

Patients were excluded if they had: contraindications to the administration of thrombolytic therapy, such as increased risk of bleeding (e.g., history of peptic ulceration, previous stroke, recent surgery, and so forth); increased risks of systemic embolism, such as a prosthetic heart valve; or protocol-specific exclusions including nondiagnostic electrocardiography because of left bundle branch block, previous coronary bypass surgery, previous administration of t-PA, or contraindication to the administration of aspirin.

Study protocol: The study was approved by the ethical review committee of each participating institution. Immediately after diagnosis and before entry to the study, patients gave full informed consent. All patients were then given soluble aspirin (300 mg orally) and an intravenous bolus injection of 5,000 IU of heparin. All patients also received an intravenous infusion of nitrates (glyceryl trinitrate or isosorbide dinitrate) titrated against systemic blood pressure that was maintained at >100 mm Hg.

All patients received a bolus dose of double-chain recombinant t-PA (duteplase, Wellcome Foundation, London) administered intravenously over 2 minutes. It was intended that the first 20 patients with angiograms suitable for analysis should receive 0.3 MU/kg of t-PA, the next 20 patients 0.45 MU/kg and the following 20 patients 0.6 MU/kg. The specific activity of this batch of t-PA was 0.3 MU/mg assessed by a clot lysis assay; therefore, the amount of protein administered to patients was approximately 1, 1.5 and 2 mg/kg, respectively, for each dose.

At the time of t-PA administration, a continuous 2-channel electrocardiographic ST-segment recording (Marquette 8000 series) was commenced and continued for 24 hours. The leads selected for recording were those that showed the greatest ST-segment changes on the 12-lead surface electrocardiogram.

Patients were taken to the cardiac catheterization laboratory where diagnostic left and right coronary arteriography was performed, and the putative infarct-related coronary artery was identified by agreement between 2 cardiologists. Selective arteriography of the infarct-related coronary artery was then performed at 60 minutes (range 60 to 70) and repeated at 90 minutes (range 90 to 100) after t-PA administration. If the infarct-related artery was considered patent (Thrombolysis in Myocardial Infarction [TIMI] perfusion grade 2 or 3)[2] by the investigators, no further interventions were performed. If patency was not achieved (TIMI grade 2 or 3) by 90 minutes after administration of t-PA, further thrombolytic or mechanical revascularization interventions were left to the discretion of the investigators.

An intravenous infusion of heparin was begun at a rate of 1,000 IU/hour at 120 minutes after the administration of t-PA. The rate of infusion was varied to achieve an activated partial thromboplastin time of 1.5 to 2 times normal. Heparin and nitrate infusions were continued for 24 hours. Soluble aspirin (300 mg) was administered daily. All other treatments were used at the discretion of the attending physician. Patients with patent infarct-related vessels had coronary arteriography repeated at 24 hours (range 20 to 36) to confirm continued patency.

Clinical and laboratory assessments: Patients were closely monitored for clinical signs of reperfusion, recurrence of myocardial ischemia, or reinfarction. Vascular invasion sites and clinical signs of possible hemorrhage were examined regularly, and patients were asked to report any untoward symptoms suggestive of bleeding. Peripheral venous blood samples were obtained at entry, and at 1, 2, 6 and 24 hours after administration of t-PA for measurement of fibrinogen and t-PA antigen.

Data analysis: In this study of a single intravenous bolus injection of t-PA, the primary end point was coronary patency at 60 and 90 minutes after treatment; to provide an indication of patency rate, it was planned that 20 patients with usable angiographic data should be entered into each dose group. Before progression to the next dose level, a committee comprising 1 member from each participating center reviewed the results with reference to safety when 16 patients had been recruited into each dose group. All patients who entered the study and received t-PA were included in the assessment of safety.

Arteriographic analysis: The infarct-related vessel on the coronary arteriogram was assessed for patency according to the classification criteria of the TIMI study group.[2] This was performed by 2 independent cardiologists in the core angiographic laboratory who were unaware of the dose of t-PA.

Electrocardiographic analysis: Continuous electrocardiographic recordings were analyzed using a computer processing system (Marquette 8000 Laser Analysis System) for the time taken after t-PA administration for the ST segment to resolve to 50% of peak displacement, and the time taken for the ST segment to return to within 0.1 mV of the isoelectric baseline.

Hemostatic analyses: Blood samples were collected in cooled tubes containing trisodium citrate (0.109 M) and immediately centrifuged at 4°C for 20 minutes at 1,600 × g. Plasma aliquots were frozen and stored at −70°C. Plasma levels of immunoreactive t-PA (t-PA antigen) were measured by a specific enzyme-linked immunosorbent assay (Imulyse t-PA Kit, Biopool, Umea, Sweden) and expressed in μg/liter. Fibrinogen concentrations were measured by clot-rate assay and expressed in g/liter.[3] The interassay coefficient of variation was <10% for both measurements.

Statistical analysis: Proportions were described using 95% confidence interval (CI) analyses. Comparisons were tested using analysis of variance or Student's *t* test. Statistical significance was defined as $p \leq 0.05$.

RESULTS

Patient characteristics: There were 24 patients entered in the first t-PA dose group, 26 in the second, and 14 in the third. The first group received a total t-PA dose of 22.5 ± 0.7 MU (range 15.1 to 28.9), the second 33.3 ± 1 MU (range 26.3 to 45.5), and the third 42.5 ± 2.5 MU (range 33.3 to 59.5).

The mean duration of chest pain at the time of t-PA administration was 3.3 ± 1.3 hours (range 0.7 to 5.9). The mean duration of symptoms was shorter in the first group (2.8 ± 0.3 hours) than in the second and third groups (3.5 ± 0.2 and 3.8 ± 0.3 hours, respectively; $p = 0.05$). There were no significant differences in age, sex, weight or delay to treatment among patients of the different treatment centers or dose groups.

History of coronary disease was present in 30 patients; 9 had a previous myocardial infarction, 16 had a history of stable angina pectoris, 10 had history of recent unstable angina, and 1 had a previous coronary angioplasty. Thirty-four patients denied any history of coronary disease. There were no significant differences

in cardiac histories among patients of different treatment centers or dose groups.

Exclusions: Nine patients who received t-PA were excluded from analysis of coronary patency for the following reasons: 2 did not have qualifying electrocardiographic criteria or definite evidence of acute myocardial infarction, 1 refused consent for angiography (which was not performed), 2 had angiography performed late (outside the 60- to 70- or 90- to 100-minute time windows), and 4 did not have usable coronary angiograms (in 1 case angiography was incomplete, in another it could not be identified because of incorrect labeling, and in 2 the angiograms could not be subsequently located for core laboratory analyses). Thus, in all, 55 cases were included in the analyses of coronary patency.

Two of the 55 cases were included in only 1 analysis of patency at 60 or 90 minutes after t-PA. One patient did not have arteriography performed within 60 to 70 minutes after t-PA, but did have it performed at 90 minutes, and another did not have arteriography performed at 90 minutes, because of resuscitation from serious arrhythmias.

All 64 patients entered in the study who received t-PA were included in the assessment of safety.

Acute coronary patency: On admission there were acute anterior electrocardiographic ST-segment changes present in 17 patients, acute inferior or inferoposterior changes in 36, and acute posterior changes in 2. The infarct-related artery was identified as the left anterior descending or its major branches in 14 cases, the left circumflex system in 10, and the right coronary artery in 31.

At 60 minutes after t-PA administration, a patent infarct-related vessel (TIMI grade 2 or 3) was present in 9 of 17 patients (53%; 95% CI 28 to 77%) who received 0.3 MU/kg, in 14 of 23 (61%; 95% CI 39 to 80%) who received 0.45 MU/kg, and in 10 of 14 (71%; 95% CI 42 to 92%) who received 0.6 MU/kg. The linear trend toward a dose-patency relation was significant ($r^2 = 0.99$; $p = 0.04$) (Figure 1).

At 90 minutes after t-PA administration, a patent infarct-related vessel (TIMI grade 2 or 3) was present in 9 of 17 patients (53%; 95% CI 28 to 77%) who received 0.3 MU/kg, in 12 of 24 (50%; 95% CI 29 to 71%) who received 0.45 MU/kg, and in 10 of 13 (77%; 95% CI 46 to 95%) who received 0.6 MU/kg. The linear trend toward a dose-patency relation was not significant ($r^2 = 0.66$; $p = 0.4$) (Figure 1). Three patients with occluded vessels at 60 minutes demonstrated patent arteries at 90 minutes (2 had received 0.3 MU/kg, and 1 had received 0.45 MU/kg). There were 5 patients with patent vessels at 60 minutes, but early reocclusions at 90 minutes (2 had received 0.3 MU/kg, and 3 had received 0.45 MU/kg).

Reocclusions and reinfarctions: Follow-up arteriography was performed at 24 hours in 30 of the 31 patients with patent vessels at 90 minutes. (One patient who received 0.6 MU/kg of t-PA and had an early patent vessel did not have arteriography repeated at 24 hours because of an acute stroke.) There was 1 documented reocclusion of the infarct-related coronary artery in each dose group: thus, the overall rate of reocclusion at 24 hours was 3 of 30 (10%; 95% CI 2 to 27%). None of these cases had clinical, electrocardiographic or enzymatic evidence of reinfarction. Two patients who both received 0.3 MU/kg of t-PA had clinical and electrocardiographic signs of reinfarction before discharge (1 at 12 hours, and 1 at 4 days). Therefore, of 30 patients with acute coronary patency, there were 5 cases (17%) of reocclusion or reinfarction before discharge.

Electrocardiography: Technically satisfactory continuous electrocardiographic ST-segment recordings were obtained from 21 patients, 11 of whom had patent infarct-related coronary arteries at 60 or 90 minutes. The mean times for the ST segments to decrease to 50% of peak displacement from the time of t-PA administration were 1.6 ± 0.6 hours in patients with patent vessels at 60 minutes, and 1.4 ± 0.6 hours in those with patent vessels at 90 minutes; the mean times for the ST segments to return to within 0.1 mV of the isoelectric line were 3.0 ± 0.7 and 2.7 ± 0.7 hours, respectively. There were no significant differences in the mean times for the ST segments to decrease to 50% of peak displacement, or to return to within 0.1 mV of the isoelectric line, among the 3 dose groups of patients with acutely patent infarct-related coronary arteries.

Hemostatic results: TISSUE-TYPE PLASMINOGEN ACTIVATOR: Plasma t-PA antigen concentrations were measured before, and at 1, 2, 6 and 24 hours after t-PA administration in 30 patients (16 from the first dose group, 8 from the second, and 6 from the third).

Plasma t-PA antigen levels recorded in the 3 dose groups up to 24 hours are shown in Figure 2. At 1 hour, significantly higher levels were found in the medium-

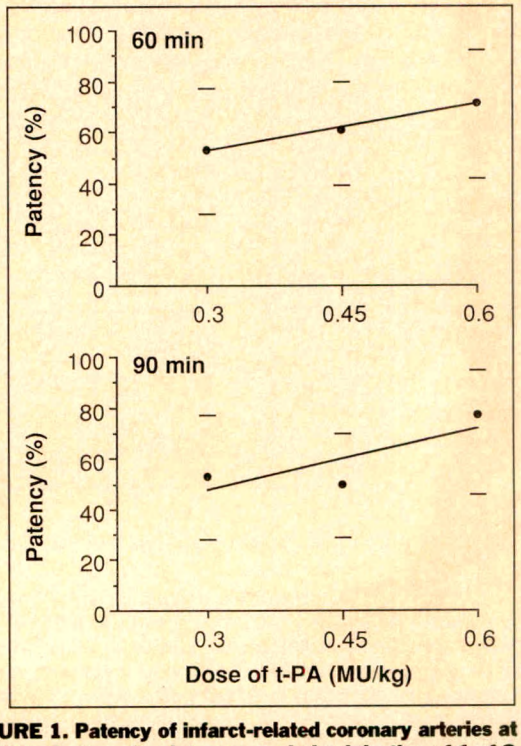


FIGURE 1. Patency of infarct-related coronary arteries at 60 and 90 minutes after intravenous bolus injection of 1 of 3 different doses of tissue-type plasminogen activator (t-PA). Means, 95% confidence intervals and linear regression lines are shown.

and high-dose groups (588.8 ± 133.0 and 341.7 ± 110.5 μg/liter, respectively) than in the lower dose group (256.4 ± 26.2 μg/liter; p = 0.034). In all 3 groups, t-PA antigen values up to 6 hours were significantly higher than those before treatment.

FIBRINOGEN: Plasma fibrinogen concentrations were measured before, and at 2 and 24 hours after t-PA administration in the same 30 patients in whom t-PA antigen was measured. (We anticipated nadir fibrinogen levels would occur within 2 hours of administration of a single bolus from a previous study in patients receiving multiple serial bolus injections of t-PA over 90 minutes.)[1]

In the 30 patients, fibrinogen levels were 3.28 ± 0.20 g/liter before t-PA administration, 2.68 ± 0.16 g/liter at 2 hours (p = 0.006 vs pretreatment), and 2.80 ± 0.13 g/liter at 24 hours (p = 0.23 vs pretreatment). No significant differences were found at any of the 3 time points between the different dose groups.

Adverse effects: There were 5 hospital deaths (7.8%) among the 64 patients entered in this study. The fatalities included 1 patient with a nonhemorrhagic stroke (confirmed by computed tomographic imaging) at 2 hours after t-PA administration who died 2 days later, 3 cases of sudden cardiogenic shock at 2, 7 and 12 hours, respectively, and 1 late sudden arrhythmic death at 7 days. Nonfatal adverse events occurred in 5 cases, including 3 serious arrhythmias and 2 renal failures (1 caused by hypotension secondary to myocardial infarction, and 1 contrast-induced toxicity with preexisting lupus nephritis). No adverse effect or death could be directly related to t-PA or thrombolytic therapy.

There were no serious bleeding events in the 64 patients entered in the study. There were 7 cases of minor oozing of blood at the catheterization site; all were managed with manual pressure over the arterial puncture site, and heparin was stopped prematurely in 2 of these cases. One patient had a small hematemesis of <100 mL, and heparin was also stopped early in this case; no other specific interventions were performed. Thus, minor bleeding complications occurred in 8 of 64 cases (12.5%).

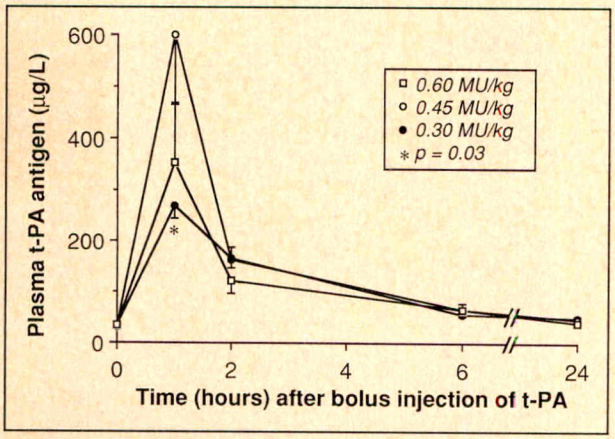


FIGURE 2. Plasma tissue-type plasminogen activator (t-PA) antigen concentrations after intravenous bolus injection of 1 of 3 different doses of t-PA. Means and SEM are shown. In all 3 groups of patients, mean plasma t-PA antigen concentrations were significantly higher up to 6 hours after bolus injection than those before treatment. At 1 hour, mean levels were significantly higher in medium- and high-dose groups than those in lower dose group.

DISCUSSION

This study shows that a single intravenous bolus injection of 0.6 MU/kg of t-PA appears to be effective and safe in inducing rapid coronary patency in patients with acute myocardial infarction. The proportion of patients in whom acute coronary patency was achieved is high and is comparable with that observed in many other patency studies that used conventional infusion regimens of t-PA (alteplase or duteplase) or other fibrinolytic agents.[4–6] The acute changes in patency observed between the 60- and 90-minute arteriograms are consistent with the dynamic nature of coronary occlusion during early thrombolysis.[7] The frequency of reocclusion at 24 hours was low and is also comparable with that observed in other studies.[8]

Several reasons prompted us to investigate the use of a single intravenous bolus injection of t-PA in patients with acute myocardial infarction. We previously demonstrated that multiple serial bolus administrations can achieve more rapid coronary patency than can a conventional intravenous infusion.[1] Several studies showed that "front-loaded" regimens of t-PA achieve acute coronary patency in a higher proportion of patients with acute myocardial infarction.[9–12] Moreover, studies using animal models of arterial thrombosis demonstrated the effectiveness of a single intravenous bolus administration of t-PA.[13–16] Furthermore, recent clinical studies of single bolus administration of t-PA to patients with acute myocardial infarction have since been reported.[17–21] Finally, the earlier the administration of thrombolytic therapy after the onset of symptoms in acute myocardial infarction, the greater the reduction in mortality; if prehospital administration of thrombolytic therapy will be widely used, then the ease and rapidity of bolus administration of a fibrinolytic agent is obvious.

Other clinical studies of bolus administration of t-PA using alteplase in patients with acute myocardial infarction reported similar results. Tebbe et al[17] reported acute coronary patency of 75% after a single bolus injection of 50 mg of alteplase. Tranchesi et al[18–19] demonstrated acute coronary recanalization in 32 to 61% of cases after single bolus injections of 50 or 60 mg and in 48 to 55% after 70 mg of alteplase. Gemmill et al[20] showed acute coronary patency in 87% of patients after two 35 mg bolus injections of alteplase. Purvis et al[21] observed acute coronary patency in 80 to 81% of cases after two 20 or 50 mg bolus injections of alteplase. The acute coronary patency results of these studies, including the present study, are broadly consistent with 95% CI that are generally overlapping. However, these results may not be strictly comparable because of the different preparations of t-PA used.

Furthermore, this study demonstrated a trend toward a dose response relation in achieving coronary

patency with bolus administration of t-PA. The first dose group of patients who received the lowest dose of t-PA had a significantly shorter duration of symptoms than did those in the second and third groups, and thus may have achieved a comparatively greater patency rate and blunted the dose-patency relation. In another study by Tranchesi et al,[18] a single intravenous bolus injection of t-PA, using 50, 60 and 70 mg of alteplase achieved coronary recanalization in 45, 32 and 72% of cases, respectively, with no trend toward a dose-response relation. However, in the present study, patients received considerably higher doses of t-PA. Our patency results of 57 to 71% are generally higher than those of Tranchesi, whereas the 95% CI remain very consistent between these studies.

Electrocardiographic manifestations of myocardial ischemia in this study quickly resolved with acute coronary patency. We previously demonstrated that the ST segments decreased to 50% of peak displacement at a mean of 1.4 hours and returned to within 0.1 mV of the isoelectric line at a mean of 2.8 hours by 90 minutes after the beginning of multiple serial bolus injections of t-PA.[1] The analogous times in this study were almost exactly the same, at 1.4 and 2.7 hours, respectively. These times for resolution of myocardial ischemia appear to be faster than those after conventional doses of intravenous infusions of t-PA.[1]

In all 3 dose groups, plasma t-PA antigen levels up to 6 hours after the bolus injection were significantly higher than those before treatment. This finding is inconsistent with the reported circulating half-life of t-PA of approximately 5 minutes and may reflect a reduced clearance rate in patients with acute myocardial infarction, or perhaps sequestration of the molecule into an extraplasmatic compartment with subsequent slow release into the circulation.[22]

We previously suggested that bolus administration compared with infusion dosing may result in higher concentrations of t-PA in plasma and thus on the coronary thrombus, resulting in earlier thrombolysis.[1] The 3 different bolus doses of intravenously administered t-PA in this study achieved different peak plasma levels and presumably different t-PA concentrations on the surface of the coronary thrombus. This may have resulted in the observed trend toward a higher acute patency rate with increasing doses of t-PA.

The systemic effects of bolus t-PA administration (assessed by fibrinogen consumption) were limited both in magnitude and duration, and appeared comparable in the 3 dose groups. The fibrinogen levels at 2 hours remained within the lower limit of the normal range (2 to 4 g/liter), and at 24 hours were not significantly lower than the pretreatment values. The in-hospital mortality of 7.8% is consistent with that expected for patients admitted with acute myocardial infarction with the entry criteria of this study. No deaths were directly attributable to t-PA, and no major bleeding complications occurred. Minor bleeding complications were infrequent (12.5%). Minor bleeding at the arterial puncture site would be expected to be frequently observed after cardiac catheterization in patients who have received any thrombolytic agent and heparin.

APPENDIX

Participants in the BEST Investigation: *Study organizer and coordinator:* David Hackett, MD, Royal Postgraduate Medical School, London, United Kingdom.

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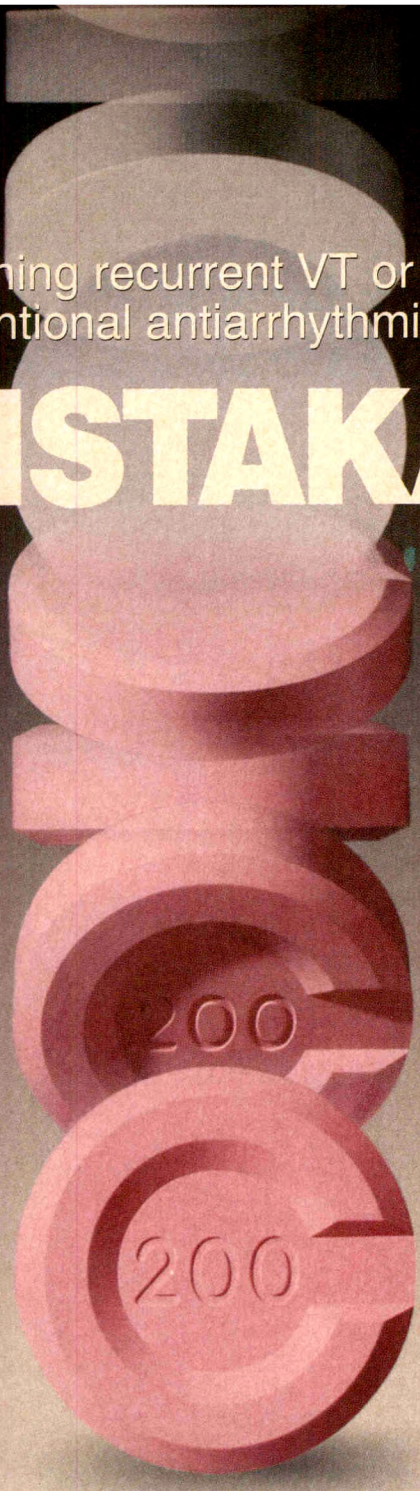
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In life-threatening recurrent VT or VF refractory
to conventional antiarrhythmic agents

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Cordarone® is intended for use only in patients with the indicated life-threatening arrhythmias because its use is accompanied by serious adverse reactions.

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Cordarone® (amiodarone HCl) Tablets

BRIEF SUMMARY
(See Package Circular for full prescribing information.)

Indications and Usage: Because of life-threatening side effects and substantial management difficulties (See "Warnings" below) use only for treating documented, life-threatening recurrent ventricular fibrillation or recurrent hemodynamically unstable ventricular tachycardia that are unresponsive to documented adequate doses of other antiarrhythmics or when alternative agents are not tolerated.

Controlled trials show no evidence that Cordarone favorably affects survival.

For use only by physicians familiar with and with access to (directly or via referral) all available modalities for treating recurrent life-threatening ventricular arrhythmias, including access to appropriate monitoring facilities and continuous electrocardiographic monitoring and electrophysiologic techniques. Due to the life-threatening nature of the arrhythmias treated, potential interactions with prior therapy, and potential arrhythmia exacerbation, start Cordarone in a hospital setting.

Contraindications: Severe sinus-node dysfunction, with marked sinus bradycardia; 2nd- and 3rd-degree atrioventricular (AV) block; episodes of bradycardia which cause syncope (except when used with a pacemaker); known hypersensitivity to the drug.

Warnings: Cordarone is intended for use only in patients with the indicated life-threatening arrhythmias because its use is accompanied by substantial toxicity.

Cordarone has several potentially fatal toxicities, the most important of which is pulmonary toxicity (hypersensitivity pneumonitis or interstitial/ alveolar pneumonitis) that has resulted in clinically manifest disease at rates as high as 10 to 17% in some series of patients with ventricular arrhythmias given doses around 400 mg/day, and as abnormal diffusion capacity without symptoms in a much higher percentage of patients. Pulmonary toxicity has been fatal about 10% of the time. Liver injury is common with Cordarone, but is usually mild and evidenced only by abnormal liver enzymes. Overt liver disease can occur, however, and has been fatal in a few cases. Like other antiarrhythmics, Cordarone can exacerbate the arrhythmia, e.g., by making the arrhythmia less well tolerated or more difficult to reverse. This has occurred in 2-5% of patients in various series, and significant heart block or sinus bradycardia has been seen in 2-5%. All of these events should be manageable in the proper clinical setting in most cases. Although the frequency of such proarrhythmic events does not appear greater with Cordarone than with many other agents used in this population, the effects are prolonged when they occur.

Even in patients at high risk of arrhythmic death, in whom the toxicity of Cordarone is an acceptable risk, Cordarone poses major management problems that could be life-threatening in a population at risk of sudden death, so that every effort should be made to utilize alternative agents first.

The difficulty of using Cordarone effectively and safely itself poses a significant risk to patients. Patients with the indicated arrhythmias must be hospitalized while the loading dose of Cordarone is given, and a response generally requires at least one week, usually two or more. Because absorption and elimination are variable, maintenance-dose selection is difficult, and it is not unusual to require dosage decrease or discontinuation of treatment. In a retrospective survey of 192 patients with ventricular tachyarrhythmias, 84 required dose reduction and 18 required at least temporary discontinuation because of adverse effects, and several series have reported 15 to 20% overall frequencies of discontinuation due to adverse reactions. The time at which a previously controlled life-threatening arrhythmia will recur after discontinuation or dose adjustment is unpredictable, ranging from weeks to months. The patient is obviously at great risk during this time and may need prolonged hospitalization. Attempts to substitute other antiarrhythmic agents when Cordarone must be stopped will be made difficult by the gradually, but unpredictably, changing amiodarone body burden. A similar problem exists when Cordarone is not effective; it still poses the risk of an interaction with whatever subsequent treatment is tried.

PULMONARY TOXICITY: Cordarone may cause a syndrome of cough and progressive dyspnea with functional, radiographic, gallium-scan and pathological data consistent with pulmonary toxicity; frequency usually varies from 2-7%, but can be as high as 10-17%. Thus, at start of therapy, perform baseline chest x-ray and pulmonary-function tests, including diffusion capacity. Repeat history, physical exam (PE), and chest x-ray every 3-6 months.

Preexisting pulmonary disease does not appear to increase risk of toxicity; however, prognosis is poorer if pulmonary toxicity develops.

Cordarone-induced pulmonary toxicity seems to result from indirect (hypersensitivity pneumonitis) or direct (interstitial/alveolar pneumonitis) toxicity.

Hypersensitivity pneumonitis usually appears early in therapy; rechallenge results in a more rapid and severe recurrence. Bronchoalveolar lavage is procedure of choice to confirm diagnosis, made when a T suppressor/cytotoxic (CD8 - positive) lymphocytosis noted. Treat with steroids and stop Cordarone.

Interstitial/alveolar pneumonitis, characterized by diffuse alveolar damage, interstitial pneumonitis or fibrosis in lung biopsies. Phospholipidosis (foamy cells, foamy macrophages) is present in most cases of Cordarone-induced pulmonary toxicity; however, this also occurs in approximately 50% of all Cordarone patients. Use these cells as therapy markers, not evidence of toxicity. If interstitial/alveolar pneumonitis is diagnosed, reduce dose or, preferably, withdraw Cordarone, especially if other acceptable antiarrhythmics are available. Where these measures were instituted, symptoms usually decreased in the first week; most clinical improvement was in first 2-3 weeks. Chest X-ray changes usually resolve in 2-4 months. Some experts feel steroids may be helpful. Prednisone (40-60 mg/day) or equivalent doses of other steroids have been used and tapered over several weeks. At times rechallenge at a lower dose will not result in return of toxicity. Reports suggest lower loading and maintenance doses are associated with a lower incidence of pulmonary toxicity.

In Cordarone patients, any new respiratory symptoms suggest a possibility of pulmonary toxicity; repeat and evaluate history, PE, chest X-ray, and pulmonary-function tests (with diffusion capacity). A 15% decrease in diffusion capacity has a high sensitivity but only a moderate specificity for pulmonary toxicity; as decreases in diffusion capacity approach 30%, sensitivity decreases but specificity increases. A diagnostic gallium scan may also be performed.

Fatalities from pulmonary toxicity occur in about 10% of cases. However, when life-threatening arrhythmias exist, stop Cordarone (amiodarone HCl) cautiously if drug-induced pulmonary toxicity is suspected. As the most common cause of death in these patients is sudden cardiac death, first rule out other causes of respiratory impairment. Bronchoalveolar lavage or lung biopsy may be necessary to confirm the diagnosis, especially when there is no acceptable alternative therapy.

If hypersensitivity pneumonitis is diagnosed, stop Cordarone and treat with steroids. If Cordarone-induced interstitial/alveolar pneumonitis is diagnosed, start steroids and, preferably, stop Cordarone or, minimally, reduce the dose. Some cases may resolve after dose reduction and steroid use. Sometimes, rechallenge at lower doses did not result in return of interstitial/alveolar pneumonitis; however, pulmonary lesions are irreversible in some.

WORSENED ARRHYTHMIA: Cordarone may cause serious exacerbation of a presenting arrhythmia, possibly enhanced by concomitant antiarrhythmic therapy. Exacerbation (about 2-5% in most series), includes new ventricular fibrillation, incessant ventricular tachycardia, increased resistance to cardioversion, and Torsade de Pointes. Cordarone has caused symptomatic bradycardia or sinus arrest with suppression of escape foci in 2-4% of patients.

LIVER INJURY: Increased hepatic enzymes, mostly asymptomatic, are seen frequently. Consider discontinuation or dose reduction if increase exceeds 3 times normal, or doubles in patient with elevated baseline. Rarely, hepatic failure has been fatal.

PREGNANCY — PREGNANCY CATEGORY D: Cordarone is embryotoxic (increased fetal resorption and growth retardation) in rats at 18 times the maximum recommended oral maintenance dose. Similar results are seen in one mice strain at about 1/2 the maximum recommended maintenance dose or higher, but not in a second strain nor rabbits at doses up to 9 times the maximum recommended maintenance dose.

Neonatal hypo- or hyperthyroidism: In utero exposure can cause fetal harm. There are some reports of congenital goiter/ hypothyroidism and hyperthyroidism. If used anytime during pregnancy apprise patient of potential fetal hazard. In general, use during pregnancy only if potential benefit to the mother justifies unknown fetal risk.

Precautions

CORNEAL MICRODEPOSITS; IMPAIRMENT OF VISION: Corneal microdeposits appear in a majority of adults on Cordarone. Usually discernible only by slit-lamp, up to 10% of patients have symptoms like visual halos or blurred vision. Microdeposits are reversible if dose reduced or treatment stopped; if asymptomatic, no need to reduce dose or stop drug.

PHOTOSENSITIVITY: Seen in about 10% of patients; sun-barrier creams or protective clothing may afford some protection. On long-term therapy, may have a blue-gray skin discoloration of exposed skin. Fair complexion or excess sun exposure may increase risk; also may be related to cumulative dose and therapy duration.

THYROID ABNORMALITIES: Cordarone inhibits conversion of thyroxine (T_4) to triiodothyronine (T_3) and may cause increased thyroxine, decreased T_3, and increased levels of inactive reverse T_3 (rT_3) in clinically euthyroid patients. Due to its release of inorganic iodine, or perhaps other reasons, Cordarone can cause either hypo- or hyperthyroidism. Monitor thyroid function before treatment and periodically thereafter, particularly in the elderly and those with history of thyroid nodules, goiter, or other thyroid dysfunction. Due to slow elimination of Cordarone and its metabolites, high plasma iodide levels, altered thyroid function, and abnormal thyroid-function tests may persist for weeks or months after withdrawal.

Hypothyroidism occurred in 2-4% of patients in most series, but in 8-10% in some. To treat, reduce Cordarone dose and/or give thyroid hormone supplement. Individualize therapy; may need to stop Cordarone.

Hyperthyroidism occurs in about 2% of patients; incidence may be higher with prior inadequate dietary iodine intake. Cordarone-induced hyperthyroidism is usually a greater hazard than hypothyroidism due to possible arrhythmia breakthrough or aggravation. IF ANY NEW SIGNS OF ARRHYTHMIA APPEAR, THE POSSIBILITY OF HYPERTHYROIDISM SHOULD BE CONSIDERED. Flat TSH response to TRH is confirmatory. Since arrhythmia breakthroughs may accompany Cordarone-induced hyperthyroidism, aggressive medical treatment is indicated, including, if possible, dose reduction or Cordarone withdrawal. Antithyroid drugs, β-blockers and/or temporary steroid therapy may be needed. (See full prescribing information for additional information regarding treatment).

SURGERY: *Hypotension Postbypass:* Rarely, hypotension is seen on cessation of cardiopulmonary bypass during open-heart surgery in Cordarone patients; relationship to Cordarone is unknown.

Adult Respiratory Distress Syndrome (ARDS): Rarely, ARDS occurs in Cordarone patients after surgery. Patients usually respond to vigorous respiratory therapy; rarely, the outcome is fatal. The mechanism may be generation of superoxide radicals during oxygenation; therefore, keep operative FiO_2 as close to room air as possible.

LABORATORY TESTS: Elevated liver enzymes (SGOT and SGPT) can occur; monitor closely if high maintenance doses used. Consider dose reduction or stopping therapy if significant elevations persist or hepatomegaly occurs.

Thyroid-function tests (increased T_4 and reverse T_3, and decreased T_3) may be altered; despite these changes, most patients remain clinically euthyroid.

DRUG INTERACTIONS: Few drug-drug interactions have been explored formally but most have shown an interaction. Thus, anticipate other interactions, especially drugs with potentially serious toxicity, like other antiarrhythmics. With its long, variable half-life, a potential for interaction also exists with drugs given after stopping Cordarone.

Digitalis: Serum digoxin increases (by up to 70%) and may reach toxic levels; onset is about 1 day. **On initiation of Cordarone, review need for digitalis and reduce its dose by about 50% or stop it.** If digitalis continued, monitor serum levels closely and observe for toxicity. Precautions probably also apply to digitoxin.

Anticoagulants: Potentiation of warfarin-type anticoagulant response is almost always seen and can result in serious or fatal bleeding. Prothrombin time may increase by 100%; onset is 3 to 4 days. **Reduce anticoagulant dose by 1/3 to 1/2, and monitor prothrombin times closely.**

Antiarrhythmic Agents: Although they have been used concurrently with Cordarone, steady-state levels of quinidine, procainamide, and phenytoin may increase during such combined therapy. Quinidine serum concentrations may increase by 33% within 2 days. Procainamide serum concentrations may increase by 55% (n-acetyl procainamide by 33%) in < 7 days. In general, reserve such combinations for patients with life-threatening ventricular arrhythmias incompletely responsive to a single agent, or incompletely responsive to Cordarone (amiodarone HCl), and start any added antiarrhythmic at a lower than usual dose with careful monitoring. During transfer to Cordarone, reduce dose of previous agents 30-50% several days after adding Cordarone, when arrhythmia suppression should be starting. After Cordarone effects are established, discontinue other antiarrhythmics if possible. If treatment is maintained, continue monitoring carefully for adverse effects, especially conduction disturbances and exacerbation of tachyarrhythmias. In Cordarone patients requiring additional antiarrhythmic therapy, initial dose of such agents should be approximately 1/2 of the usual dose.

Use Cordarone cautiously with β-blockers or calcium antagonists as bradycardia, sinus arrest, and AV block may be potentiated; if necessary, Cordarone can continue after pacemaker insertion in patients with severe bradycardia or sinus arrest.

ELECTROLYTE DISTURBANCES: May be ineffective or arrhythmogenic if hypokalemia is present; correct any potassium or magnesium deficiency before starting drug.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY: Fertility reduced in male and female rats at 8 x the highest recommended human maintenance dose. Cordarone caused a statistically significant, dose-related increase in thyroid tumors in rats. Incidence greater than control even at lowest dose tested, i.e., about 1/2 the highest recommended human maintenance dose. Mutagenicity studies were negative.

PREGNANCY: PREGNANCY CATEGORY D — See **Warnings.**

LABOR AND DELIVERY: Occurrence of adverse effects during labor or delivery is unknown. Preclinical studies in rodents have shown no effect on gestation duration or parturition.

NURSING MOTHERS: Cordarone is excreted in human milk; breast-feeding may expose nursing infants to a significant drug dose. Nursing offspring of lactating rats given Cordarone were less viable and had reduced body-weight gains. Advise mothers to discontinue nursing before taking.

PEDIATRIC USE: Safety and effectiveness have not been established.

Adverse Reactions: Adverse effects are very common (about 3/4 of all patients) with doses of 400 mg/day or more, and cause 7-18% to discontinue. The most serious are pulmonary toxicity, arrhythmia exacerbation, and rare serious liver injury (see "**Warnings**"), but other adverse effects constitute important problems. They are often reversible by reducing dose and virtually always reversible by stopping Cordarone. Most adverse effects appear more frequent with continued treatment beyond 6 months; rates appear relatively constant beyond one year. Neurologic problems, including malaise and fatigue, tremor and involuntary movements, poor coordination and gait, and peripheral neuropathy are common (20-40% of patients); these may respond to dose reduction, rarely need to stop therapy.

Gastrointestinal (GI) complaints, commonly seen with high doses (i.e., loading dose), usually respond to dose reduction or divided doses; rarely need to stop drug.

Asymptomatic corneal microdeposits. See **Precautions** and full prescribing information.

Photosensitivity. See **Precautions** and full prescribing information.

Cardiovascular adverse reactions, other than arrhythmia exacerbation, include the uncommon occurrence of congestive heart failure (3%) and bradycardia. Bradycardia usually responds to dose reduction but may require a pacemaker. CHF rarely requires stopping drug. Cardiac conduction abnormalities occur infrequently and are reversible upon stopping drug.

The following side-effect rates are based on a retrospective study of 241 patients treated for 2 to 1,515 days (mean 441.3 days).

Each reported in 10-33% of patients: GI–Nausea and vomiting.

Each reported in 4-9% of patients: Dermatologic–Solar dermatitis/photosensitivity; Neurologic–Malaise and fatigue, tremor/abnormal involuntary movements, lack of coordination, abnormal gait/ataxia, dizziness, paresthesias; GI–Constipation, anorexia; Ophthalmologic–Visual disturbances; Hepatic–Abnormal liver-function tests; Respiratory–Pulmonary inflammation or fibrosis.

Each reported in 1-3% of patients: Thyroid–Hypo- or hyperthyroidism; Neurologic–Decreased libido, insomnia, headache, sleep disturbances; Cardiovascular–CHF, cardiac arrhythmias, SA node dysfunction; GI–Abdominal pain; Hepatic–Nonspecific hepatic disorders; Other–Flushing, abnormal taste and smell, edema, abnormal salivation, coagulation abnormalities.

Each reported in < 1% of patients: Blue skin discoloration, rash, spontaneous ecchymosis, alopecia, hypotension, and cardiac conduction abnormalities. Rarely hepatitis, cholestatic hepatitis, cirrhosis, optic neuritis, epididymitis, vasculitis, pseudotumor cerebri, and thrombocytopenia.

Adverse reactions most frequently requiring Cordarone discontinuation include pulmonary infiltrates or fibrosis, paroxysmal ventricular tachycardia, CHF, and elevated liver enzymes. Symptoms causing discontinuation less often include visual disturbances, solar dermatitis, blue skin discoloration, hyper- or hypothyroidism.

Overdosage: The few reports of Cordarone overdose, in which 3 to 8 grams were taken, resulted in no deaths or permanent sequelae. Animal studies indicate that Cordarone has a high oral LD_{50} (>3,000 mg/kg).

Along with general supportive measures, monitor patient's cardiac rhythm and blood pressure; if bradycardia ensues, may use a β-adrenergic agonist or pacemaker. Use positive inotropic and/or vasopressor agents to treat hypotension with inadequate tissue perfusion. Neither Cordarone nor its metabolite is dialyzable.

Dosage and Administration: See full prescribing information.

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Philadelphia, PA 19101

4008-2 Revised October 18, 1990

Beneficial Effect of Amiodarone on Cardiac Mortality in Patients with Asymptomatic Complex Ventricular Arrhythmias After Acute Myocardial Infarction and Preserved But Not Impaired Left Ventricular Function

Matthias Pfisterer, MD, Wolfgang Kiowski, MD, Dieter Burckhardt, MD, Ferenc Follath, MD, and Felix Burkart, MD

To determine whether the beneficial effect of low-dose amiodarone on survival in patients with complex ventricular arrhythmias after myocardial infarction was dependent on left ventricular (LV) function, results of the Basel Antiarrhythmic Study of Infarct Survival were analyzed. Two hundred twelve patients after acute myocardial infarction with asymptomatic complex arrhythmias were randomly assigned to receive amiodarone 200 mg/day or to a control group and followed up for 1 year. Results of mortality and arrhythmic events were related to baseline radionuclide LV ejection fraction. With preserved (≥40%) LV ejection fraction, there was a significantly lower 1-year cardiac mortality in patients treated with amiodarone (1 of 68 or 1.5%) versus control subjects (5 of 56 or 8.9%; p <0.03). This was not the case for patients with LV ejection fraction <40%. Similarly, arrhythmic events were significantly reduced only in patients with preserved LV function. These results suggest an interaction between the effects of amiodarone on survival and LV dysfunction in patients after acute myocardial infarction. Because of 2 other small studies with similar results, this finding may be of clinical relevance and should be addressed in ongoing and future research with this drug.

(Am J Cardiol 1992;69:1399–1402)

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The hypothesis that survival in patients with asymptomatic complex ventricular arrhythmias after acute myocardial infarction can be improved by antiarrhythmic therapy was not substantiated by several studies,[1] the last being the Cardiac Arrhythmia Suppression Trial (CAST).[2] The Basel Antiarrhythmic Study of Infarct Survival (BASIS) confirmed these findings for class I antiarrhythmic drugs. However, it demonstrated for the first time a beneficial effect on survival in such patients treated with low-dose amiodarone.[3] These results were confirmed by the Canadian Amiodarone in Myocardial Infarction Trial (CAMIAT) pilot study[4] and prompted a series of large prospective trials with amiodarone after myocardial infarction. The main CAMIAT project will study the effect of amiodarone on survival in patients after myocardial infarction with high-grade ventricular ectopic activity irrespective of left ventricular (LV) function; the European Myocardial Infarction Amiodarone Trial will assess whether amiodarone may improve survival in patients after myocardial infarction and reduced LV function irrespective of ventricular arrhythmias; a Veterans Administration Amiodarone Trial in the USA is evaluating the effects of amiodarone on mortality and arrhythmic events in patients with complex ventricular ectopic activity and depressed LV ejection fraction. In view of these studies, it seemed appropriate to address the question of whether the beneficial effect of amiodarone observed in the BASIS study was dependent on LV ejection fraction.

METHODS

Study protocol: The methods used in the BASIS study have previously been described in detail.[3,5] In short, survivors of myocardial infarction with asymptomatic complex ventricular arrhythmias persisting at hospital discharge (Lown grade III to IVb arrhythmias in at least 2 of 24 hours of Holter electrocardiographic recording) were randomized into 3 treatment groups: (1) individualized antiarrhythmic therapy starting with class I antiarrhythmic drugs, (2) low-dose amiodarone (200 mg/day after an initial loading dose of 1,000 mg for 5 days), and (3) a control group without antiarrhythmic therapy. For the present analysis, only patients in groups B and C were considered. Radionuclide

TABLE I Baseline Patient Characteristics

	Amiodarone		Control	
LVEF Groups	≥40%	<40%	≥40%	<40%
No. of pts.	68	30	56	58
% men	79	83	84	86
Age	60 ± 8	62 ± 7	61 ± 7	62 ± 6
% previous AMI	32	50	36	62
% anterior AMI	38	59	36	52
LVEF	53 ± 9	28 ± 8	56 ± 11	27 ± 10
VPG/hour	41 ± 77	81 ± 136	20 ± 50	67 ± 162
% ≥10 VPG/hour	41	60	34	66
% Lown IV	57	63	48	76

AMI = acute myocardial infarction; VPCs = ventricular premature complexes; LVEF = left ventricular ejection fraction.

LV ejection fraction was determined at rest before starting therapy. For this analysis, preserved LV function had been defined in advance as LV ejection fraction of ≥40% and impaired LV function as LV ejection fraction <40%. All patients were followed after 3, 6 and 12 months in the outpatient clinic. A small subgroup of patients (29 taking amiodarone and 18 control patients) consented to a repeat radionuclide study after 1 year.

Patients: Two hundred twelve patients (84% men, mean age 61 ± 7 years) who fulfilled the entry criteria and consented to the study protocol were included in the study. They were randomized into 2 groups: 98 to amiodarone therapy and 114 to the control group.

Analysis: All data were analyzed according to intention-to-treat. Data are presented as mean values ± 1 standard deviation and as frequencies where appropriate. Comparisons were performed using the Student's *t* test for unpaired samples and the chi-square test. Survival curves were drawn according to the Kaplan-Meier life table analysis. Differences and proportions with a 2-tailed *p* value <0.05 were considered significant. Calculations were performed with the use of the SYSTAT statistical program.

RESULTS

Patient characteristics: Patient characteristics in the 2 treatment groups in relation to LV function are listed in Table I. In both groups, patients with impaired LV function had a higher rate of previous and anterior infarcts and a greater average number of ventricular premature beats per hour. Otherwise there were no significant differences between both treatment groups.

Effect on mortality and arrhythmic events: Total 1-year mortality according to actuarial life table analysis was 5 of 98 (5.1%) for amiodarone and 15 of 114 (13.2%) for control patients ($p < 0.05$). This would relate to savings of 8 lives per 100 treated patients over 1 year. If subdivided according to LV ejection fraction at entry, this beneficial effect was also observed in patients with preserved LV function (Figure 1): There was a significant reduction in 1-year cardiac mortality from 5 of 56 (8.9%) in the control group to 1 of 68 (1.5%) in those taking amiodarone (reduction by 7.4% [95% confidence interval 1.3%/13.5%; $p < 0.03$]). No such effect was seen in patients with impaired LV function (mortality 8 of 58 [13.8%]) in the control group versus 4 of 30 (13.3%) taking amiodarone (difference 0.5% [95% con-

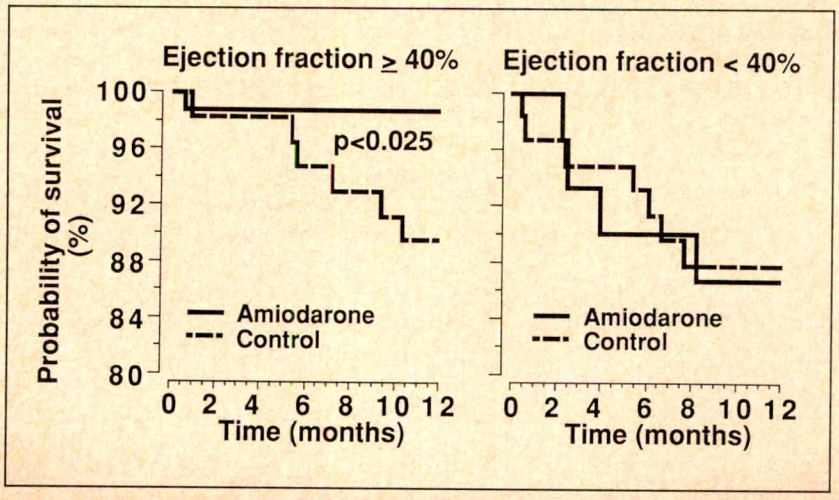


FIGURE 1. Probability of survival in patients taking amiodarone versus control subdivided according to baseline left ventricular (LV) ejection fraction ≥ and <40%, respectively. There was a significantly better survival only in patients with LV ejection fraction ≥40%.

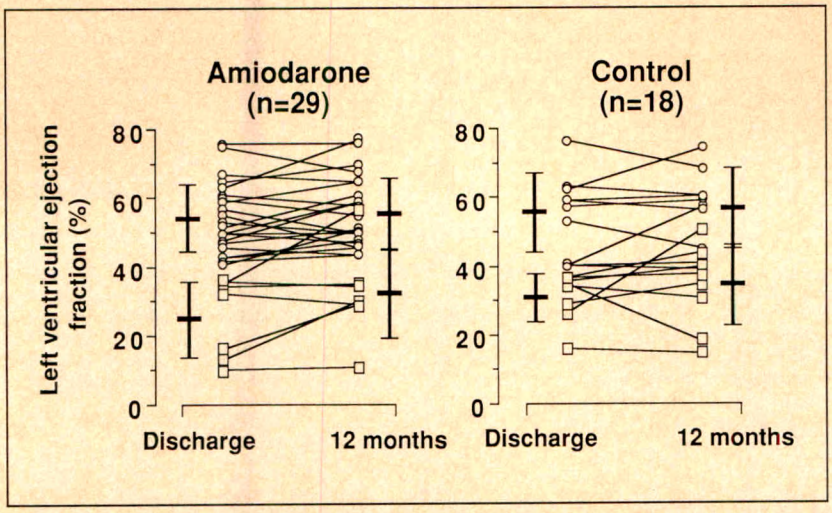


FIGURE 2. Change in left ventricular (LV) ejection fraction in the first year after myocardial infarction in the 2 subgroups of patients taking amiodarone and in the control group, respectively. No negative inotropic effect of amiodarone was observed. *Circles*, LV ejection fraction ≥40%; *squares*, LV ejection fraction <40%.

fidence interval 14.3%/15.3%; p = not significant]). These findings were in accordance with the effects of amiodarone on arrhythmic events defined as sudden cardiac death, successfully resuscitated ventricular fibrillation or sustained (>10 beats) ventricular tachycardia on control Holter recordings. In patients with preserved LV function, there were significantly fewer arrhythmic events in those taking amiodarone (1.5%) than in the control group (12.5%; p <0.03), whereas in patients with LV ejection <40% this difference was much smaller and not significant (19.0 vs 16.7%).

Arrhythmia suppression and hemodynamic effects: To identify potential underlying mechanisms for the discrepant effects of amiodarone in relation to LV function, the degree of arrhythmia suppression and changes in LV ejection fraction over time were analyzed in both groups. Amiodarone decreased the mean number of ventricular premature complexes per hour by −20, +21 and −68% after 3, 6 and 12 months in patients with LV ejection fraction ≥40%, and by −73, −53 and −49%, respectively, in patients with an LV ejection fraction <40% (p = not significant between groups). In addition, the effect of amiodarone on LV ejection fraction was not different between patients with preserved and impaired LV function (Figure 2). Interestingly, amiodarone did not exhibit any negative inotropic effect in this study over the 1-year period.

DISCUSSION

The main finding of this analysis is that the beneficial effect of amiodarone on survival in patients with persisting asymptomatic complex ventricular arrhythmias after myocardial infarction as described in the BASIS study[3] seemed to be confined to patients with preserved LV function. The antiarrhythmic potency of amiodarone has been demonstrated in patients with and without congestive heart failure.[6,7] This antiarrhythmic effect was rather small in the present study and similar for both subgroups and may not explain the observed difference in mortality. Therefore, antifibrillatory,[8] antiadrenergic[9] or anti-ischemic[10] properties of amiodarone could play a dominant role here. This does not explain why this effect was limited to patients with preserved LV function. Neither a negative inotropic nor a significant proarrhythmic effect was found that could have blunted a beneficial trend in the higher risk group of patients with a LV ejection fraction <40%. However, as has been suggested before,[11] the prognostic importance of LV ejection fraction may well become paramount to that of ventricular arrhythmias with decreasing LV function.

Study limitations: The present findings represent a subanalysis of a prospective randomized trial with a relatively small number of patients. Although this subanalysis was planned ahead, patients were not randomized to separate groups with preserved and depressed LV function. Thus, these findings have to be interpreted with great caution since unrecognized confounding factors may have influenced the results. However, our observations of an interaction between the effects of amiodarone on survival and LV dysfunction have been confirmed recently by 2 small studies[12,13] and may thus have important implications for ongoing and future research in this field.

Acknowledgment: Radionuclide studies were performed in cooperation with the Division of Nuclear Medicine (Jan Müller-Brand, MD). We acknowledge the technical assistance of Hanka Jordi and the secretarial skills of Cathy Faes.

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Incidence and Timing of Recurrences of Sudden Death and Ventricular Tachycardia During Antiarrhythmic Drug Treatment After Myocardial Infarction

Luz Maria Rodriguez, MD, Joep Smeets, MD, Gilles E. O'Hara, MD, Peter Geelen, MD, Pedro Brugada, MD, and Hein J. J. Wellens, MD

Incidence and timing of recurrences of sustained ventricular tachycardia (VT) or sudden death were studied in 206 patients who survived their first episode of ventricular fibrillation (VF; n = 52) or sustained VT (n = 154) after myocardial infarction. All patients were treated with (empirically selected) antiarrhythmic drugs; 49% received amiodarone. After a mean follow-up of 36 months, 64 patients (41%) in the VT group and 10 (19%) in the VF group had nonfatal VT recurrences. Sudden death occurred in 22 (14%) and 9 (17%) patients in the VT and VF groups, respectively.

Incidence of sudden death had 2 peaks at approximately 3 and 12 months. Nonfatal VT recurrences were more frequent (most often occurring in first 6 months) in the VT than in the VF group. Sudden death occurred during the following 3 years in only 10% of patients who survived 1 year. There was a much higher incidence of sudden death in patients with left ventricular ejection fraction (LVEF) ≤40% than in those with LVEF >40% (28 of 65 vs 3 of 141; p <0.0001), but no relation between LVEF and nonfatal VT recurrences.

(Am J Cardiol 1992;69:1403–1406)

The long-term treatment of life-threatening ventricular arrhythmias outside the acute phase of myocardial infarction remains a major challenge. Follow-up of these patients reveals that many die suddenly or have nonfatal arrhythmia recurrences. This has been well-documented for patients with out-of-hospital sudden death and sustained ventricular tachycardia (VT).[1–7] Less is known about the time course of recurrences of sudden death and sustained VT in these patients. We retrospectively analyzed 206 patients who had a well-documented episode of sustained VT or ventricular fibrillation (VF) late after a myocardial infarction and who were treated with antiarrhythmic drugs only.

METHODS

Two hundred six consecutive patients who had a previous myocardial infarction and either developed VT (n = 154) or were resuscitated from VF (n = 52) were included in this study. In the VT group, there were 129 men and 25 women (mean age 59 ± 9 years). In the VF group, there were 43 men and 9 women (mean age 58 ± 12).

Evaluation of these patients on admission included clinical history, physical examination, 12-lead electrocardiogram, long-term electrocardiographic monitoring, exercise testing and programmed electrical stimulation of the heart while off and on antiarrhythmic drug treatment. Left ventricular ejection fraction (LVEF) was obtained using various techniques including nuclear or contrast angiography and 2-dimensional echocardiography. Coronary angiography was performed at our institution or the referring hospital.

Antiarrhythmic drug therapy was empirically selected (not by serial drug testing), because patients were included in the "parallel study." This approach was described in detail elsewhere.[8] Briefly, patients admitted with an episode of VT or VF were continuously monitored in the coronary care unit. After washout of antiarrhythmic drug therapy (if present), patients underwent baseline studies including exercise testing, echocardiography and programmed electrical stimulation. These tests were repeated after institution of antiarrhythmic drug therapy that was empirically selected. Antiarrhythmic therapy was continued until a spontaneous recurrence of the ventricular arrhythmia was observed. Inducibility of an arrhythmia during programmed electrical stimulation did not influence the antiarrhythmic

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TABLE I Clinical Characteristics of Patients Studied

	VT	VF	p Value
Age (yr)	59 ± 9	58 ± 12	NS
Men/women	129/25	43/9	
Symptoms of clinical arrhythmia			
Minimal	64 (42%)		
Syncope	90 (58%)		
Cardiac arrest		52 (100%)	
NYHA dyspnea			
Class I	52 (34%)	12 (23%)	NS
Class II	67 (44%)	17 (33%)	NS
Class III	35 (22%)	23 (44%)	<0.009
NYHA angina			
Class I	77 (50%)	30 (58%)	NS
Class II	42 (27%)	12 (23%)	NS
Class III	35 (23%)	10 (19%)	NS
Time interval MI-VT/VF			
>2 months	89 (57%)	19 (37%)	<0.007
<2 months	66 (43%)	33 (63%)	<0.02
Location of MI			
Anterior	53 (34%)	20 (38%)	NS
Multiple sites	33 (22%)	12 (23%)	NS
LVEF (mean) (%)	36 ± 7	30 ± 10	<0.005

LVEF = left ventricular ejection fraction; MI = myocardial infarction; NS = not significant; NYHA = New York Heart Association; VF = ventricular fibrillation; VT = ventricular tachycardia.

TABLE II Angiographic Data

	VT	VF	p Value
Number of coronary arteries narrowed >50% in diameter			
1	78 (50%)	7 (14%)	<0.008
2	48 (31%)	12 (23%)	NS
3	21 (14%)	30 (58%)	<0.0001
Unknown	7 (5%)	3 (5%)	NS
LVEF ≤40%	49 (32%)	16 (31%)	NS
LVEF >40%	105 (68%)	36 (69%)	NS
LV aneurysm	69 (45%)	30 (58%)	NS

Abbreviations as in Table I.

regimen. Only spontaneous recurrences of VT/VF during the treatment period were reasons to change the antiarrhythmic drug regimen. Patients were followed up at our outpatient clinic at regular intervals. Mean follow-up was 36 months (range 1 to 108).

Definitions: SUDDEN DEATH: Sudden unexpected death occurring within 1 hour of onset of symptoms.

SUDDEN ARRHYTHMIC DEATH: Death caused by a recurrent arrhythmia, even when death occurred >1 hour after onset of arrhythmia.

RECURRENT VENTRICULAR TACHYCARDIA: Sustained monomorphic VT occurring spontaneously out-of-hospital during follow-up.

Statistical analysis: Continuous data are expressed as mean ± SD. Comparison of the clinical characteristics between subgroups was obtained by chi-square test, using Yates correction when appropriate. A p value <0.05 was considered significant. Kaplan-Meier actuarial curves[9] for sudden death and nonfatal VT recurrences were constructed. Actuarial recurrences for sudden death and nonfatal VT recurrences for the VT and VF groups were compared using Wilcoxon and log rank tests.

TABLE III Antiarrhythmic Drug Treatment

Antiarrhythmic Drug	Patients (%)
Type IA*	15 (7)
Type IB†	7 (3.5)
Type IC‡	43 (21)
Type IV§	5 (3)
Amiodarone	70 (34)
Amiodarone + combination	31 (15)
Sotalol	15 (7)
Combination	11 (5.5)
No drugs	9 (4)

*Procainamide, quinidine and disopyramide.
†Mexilitine and aprindine.
‡Flecainide and propafenone.
§Bepridil.

TABLE IV Antiarrhythmic Drug and Nonfatal Ventricular Tachycardia Recurrences

Antiarrhythmic Drug	VT Recurrences (no. of pts.)
Amiodarone	30
Amiodarone + combination	6
Type IA	7
Type IB	4
Type IC	16
Type IV	2
Sotalol	2
Combination	7

p = not significant.
VT = ventricular tachycardia.

RESULTS

The clinical and angiographic characteristics of the VT and VF groups are listed in Tables I and II. Sustained VT while off antiarrhythmic drug therapy could be induced in 140 of 154 patients (91%) in the VT group and in 43 of 52 (83%) in the VF group.

Antiarrhythmic drug therapy: One hundred one patients (49%) received amiodarone (mean dose 260 mg) alone or in combination with other antiarrhythmic drugs, 15 patients (7%) received sotalol (range 40 to 420 mg/day), 33 (16%) received propafenone (450 to 900 mg/day), 10 (5%) received procainamide (750 to 3,000 mg/day), 1 received quinidine (1,200 to 1,600 mg/day), 4 received disopyramide (300 to 600 mg/day), 10 (5%) received flecainide (100 to 200 mg/day), 3 received aprindine, (50 to 150 mg/day), 4 received mexilitine (200 to 300 mg), and 5 received bepridil (200 to 600 mg). Nine patients (4%) had no antiarrhythmic drug therapy, and the remaining 11 (5%) received a combination of antiarrhythmic drugs (Table III).

Nonfatal recurrences occurred in 36 of 101 patients (36%) treated with amiodarone and in 38 of 105 (36%) treated with another antiarrhythmic drug (p = not significant [NS]) (Table IV).

Of the 206 patients, 171 underwent programmed electrical stimulation while receiving antiarrhythmic drugs; 122 of 171 (71%) were inducible, and 49 (29%) were not inducible. Nonfatal VT recurrences occurred

in 49 of 122 inducible patients (40%) and in 16 of 49 noninducible patients (33%) (p = NS). Sudden death occurred in 18 of 122 inducible patients (17%) and in 8 of 49 noninducible patients (16%) (p = NS).

Nonfatal ventricular tachycardia recurrences: After a mean follow-up of 36 months, 64 patients (41%) in the VT group, and 10 (19%) in the VF group had nonfatal recurrences of sustained VT. These recurrences occurred more frequently in the first 6 months in the VT than in the VF group (Wilcoxon 0.03) (Figure 1).

Actuarial curves for nonfatal recurrences of sustained VT for the VT and VF groups were constructed (Figure 2). At 1, 2, 3, 4 and more years, nonfatal recurrences occurred at rates of 10, 12, 13, 7 and 4%, respectively, in the VT group, and 13, 5, 8, 0 and 4%, respectively, in the VF group.

A second VT recurrence was observed in 27 (17%) and 3 (1.5%) patients in the VT and VF groups, respectively. A third VT recurrence occurred in 7 patients (3%) in the VT group. A fourth recurrence was present in only 1 patient in the VT group. No patient in the VF group had >2 recurrences.

Nonfatal VT recurrences were observed in 20 of 65 patients (31%) with LVEF ≤40% and in 54 of 141 patients (38%) with LVEF >40% (p = NS).

Sudden death: Twenty-two patients (14%) in the VT group and 9 (17%) in the VF group (p = NS) died suddenly. The VT group had 2 peaks at 3 and 12 months, and the VF group at 3 months and approximately 18 months (Figure 3). In patients who survived 1 year, sudden death occurred in only 10% during the following 3 years.

Actuarial curves for sudden death in the VT and VF groups are shown in Figure 4. At 1, 2, 3, 4 and 5 years, sudden death occurred at rates of 10, 6, 2, 2 and 0%, respectively, in the VT group. In the VF group, the rates were 12, 6, 4, 0 and 0%, respectively. Although the incidence of sudden death was higher in the VF group, there was no statistical significance with the VT group (Wilcoxon 0.10) (Figure 4).

Sudden death occurred more often in patients with LVEF ≤40% (28 of 65; 43%) than in those with LVEF >40% (3 of 141; 2%) (p <0.0001).

Arrhythmic events (nonfatal VT recurrence and sudden death) were present in similar rates in responders (noninducible or nonsustained VT during programmed electrical stimulation on drugs, and no arrhythmic events) (16 of 33; 48%) and nonresponders (inducible VT and arrhythmic events) (29 of 54; 53%) (p = NS) treated with amiodarone.

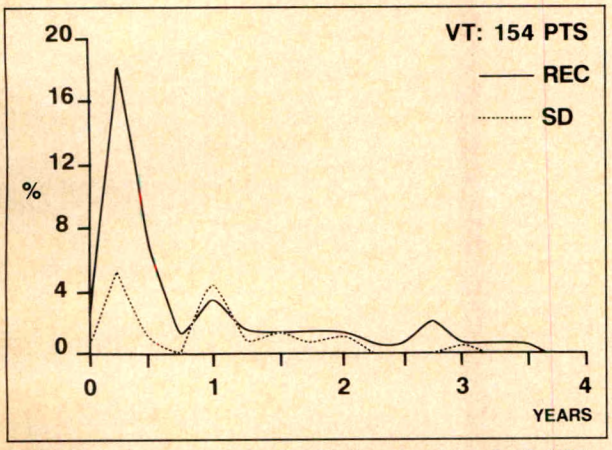


FIGURE 1. Curves representing timing of sudden death (SD) and nonfatal ventricular tachycardia (VT) recurrences (REC) in patients who had sustained ventricular tachycardia as their first arrhythmic event.

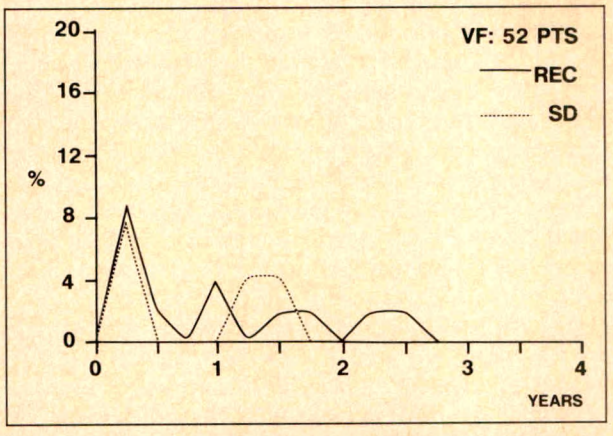


FIGURE 3. Curves showing timing of sudden death (SD) and nonfatal ventricular tachycardia recurrences (REC) in patients who had ventricular fibrillation (VF) as their first arrhythmic event.

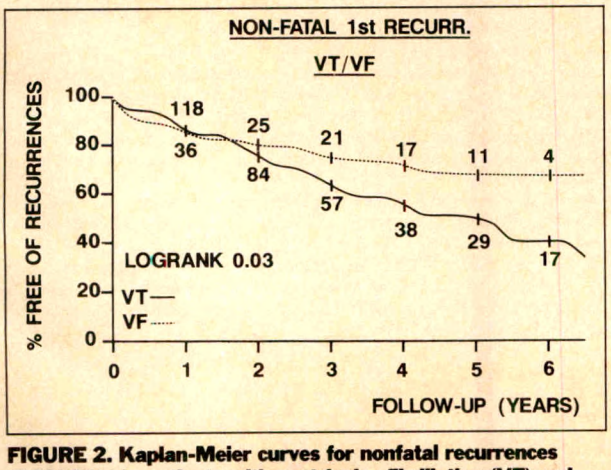


FIGURE 2. Kaplan-Meier curves for nonfatal recurrences (RECURR.) in patients with ventricular fibrillation (VF) and ventricular tachycardia (VT).

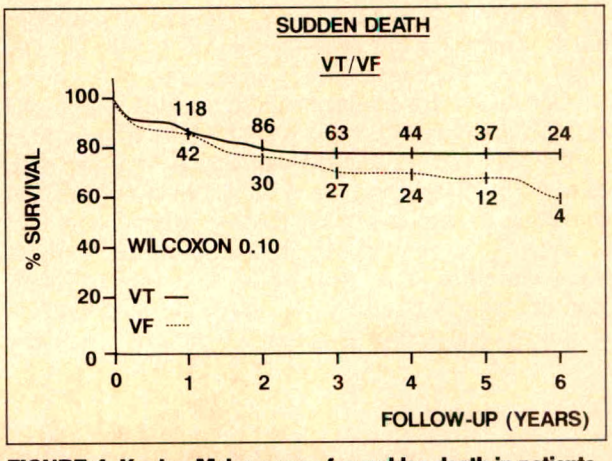


FIGURE 4. Kaplan-Meier curves for sudden death in patients with sustained ventricular tachycardia (VT) and ventricular fibrillation (VF).

DISCUSSION

The first studies in the early 1970s of out-of-hospital cardiac arrest survivors reflect the poor prognosis of patients with coronary heart disease and cardiac arrest remote from acute myocardial infarction. These studies reported recurrence rates of 30 to 36% in the first year, decreasing to 10 to 15% in the second year. More recently, 2 studies in which patients were receiving long-term antiarrhythmic drug therapy guided by electrophysiologic testing demonstrated an improvement in cardiac arrest recurrences (14% at 1 year, and 22% at 3 years).[10–12] In these studies, recurrences rates for cardiac arrest showed 2 phases (early and late); the cumulative recurrence rate was 10 to 15% in the first year, decreasing to 5% in the following year.[11,12]

Furukawa et al[13] found recurrent cardiac arrest in patients with chronic coronary artery disease who survived out-of-hospital cardiac arrest in the absence of acute myocardial infarction to have an incidence of 14, 6.5, 1.6 and 1.8% at 1, 2, 3 and 4 years, respectively, with a cumulative actuarial rate at 4 years of 24 ± 5%. In that study, most patients were receiving antiarrhythmic drugs, with only a small group treated with antiarrhythmic surgery or an automatic implantable defibrillator.

Swerdlow et al[6] reported actuarial curves for sudden death at 6 months, and 1, 2 and 3 years with rates of 12, 17, 25 and 36%, respectively. However, in their study they also included patients with valvular disease and no structural heart disease. Winkle et al[14] reported actuarial curves for sudden death in patients receiving an automatic implantable defibrillator of 0.9, 3.1, 4.4, 4.4 and 4.4% at 1, 2, 3, 4 and 5 years, respectively. They found extremely low 1- and 2-year sudden death rates in patients receiving an automatic implantable defibrillator.

Our patients that were treated with antiarrhythmic drug therapy only had a peak of sudden death at 3 months. A second peak in sudden death was observed at 12 months in the VT group and at 18 months in the VF group. In patients who survived 1 year, sudden death occurred in only 10% during the following 3 years. Actuarial curves for sudden death showed rates of 10, 6, 2, 0 and 0% in the VT group, and 12, 6, 4, 0 and 0% in the VF group at 1, 2, 3, 4 and 5 years, respectively. Sudden death occurred more often in the VF group, but the difference was not statistically significant.

Our results are similar to those reported after 1 (12 vs 14%) and 4 (22 vs 24%) years by Furukawa et al.[13]

Currently, little attention has been given to the time course of nonfatal recurrences of VT. In our population consisting of coronary artery disease patients only and of whom 49% were treated with amiodarone, nonfatal VT recurrences were more often seen in the first 6 months (Figures 1 and 2). The actuarial curves indicate a similar incidence of nonfatal VT recurrences in the VT and VF groups during the first 2 years (Figure 2). Thereafter, more VT recurrences were observed in the VT group. Herre et al[15] reported a recurrence rate of VT or VF at 1, 2, 3, 4 and 5 years of 19, 7, 7, 8 and 2%, respectively (cumulative rate at 5 years: 43%). However, their patients included not only those with coronary artery disease, but also those with no structural heart disease and right ventricular dysplasia. All their patients received long-term treatment with amiodarone.

Comparison of long-term outlook of ventricular tachycardia and fibrillation patients: Our data indicate that in a group of patients with the same etiology of heart disease, a higher incidence of sudden death was present in the VF than in the VT group. The data also show that 1 year after an episode of sustained VT or VF after myocardial infarction, the risk of dying suddenly is relatively low. This information can be useful in selecting the type of antiarrhythmic therapy for patients who have had VT/VF remote from the acute phase of a myocardial infarction.

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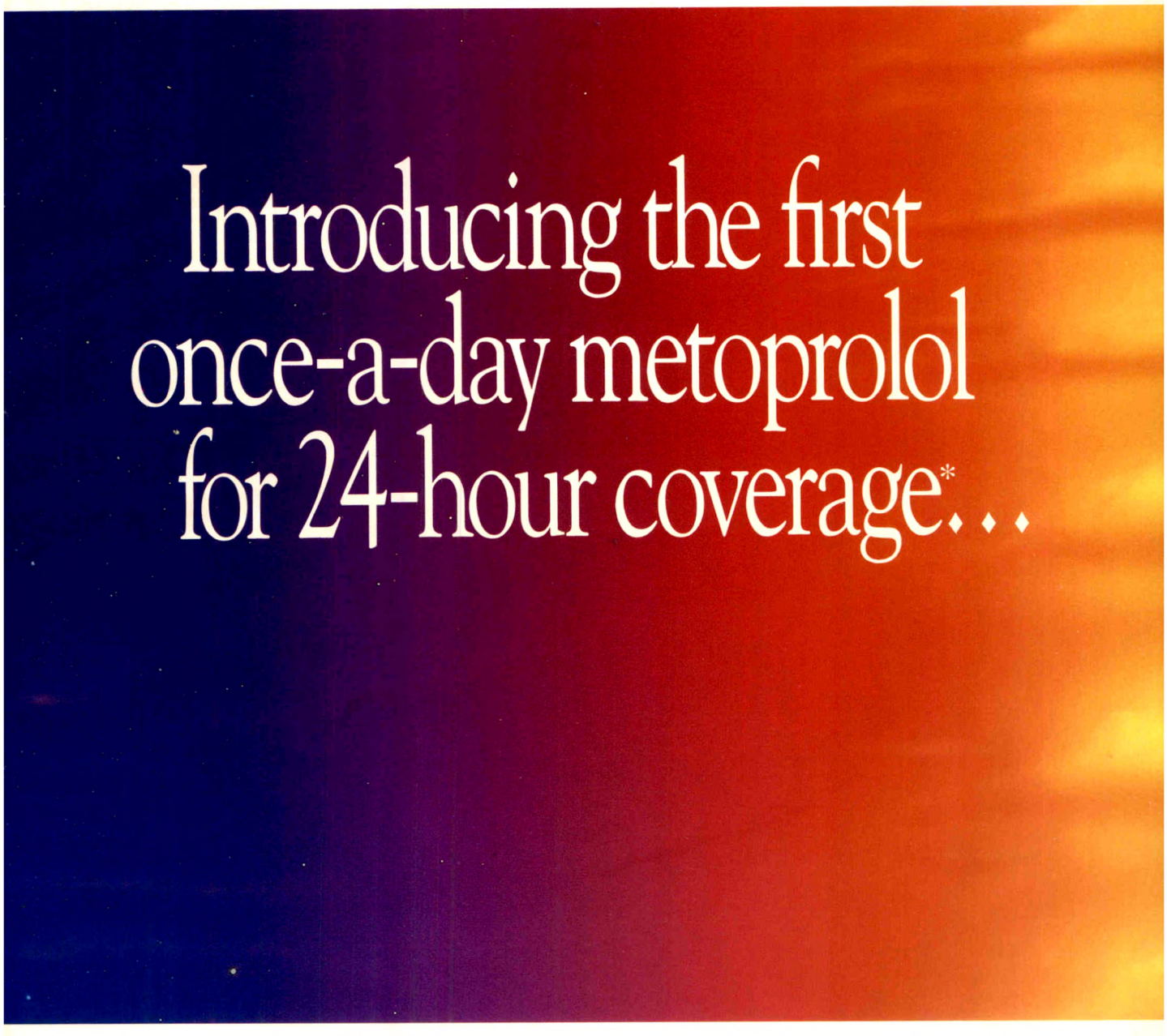
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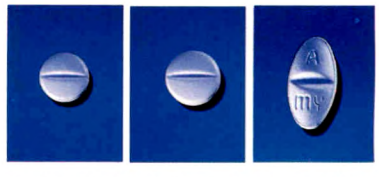
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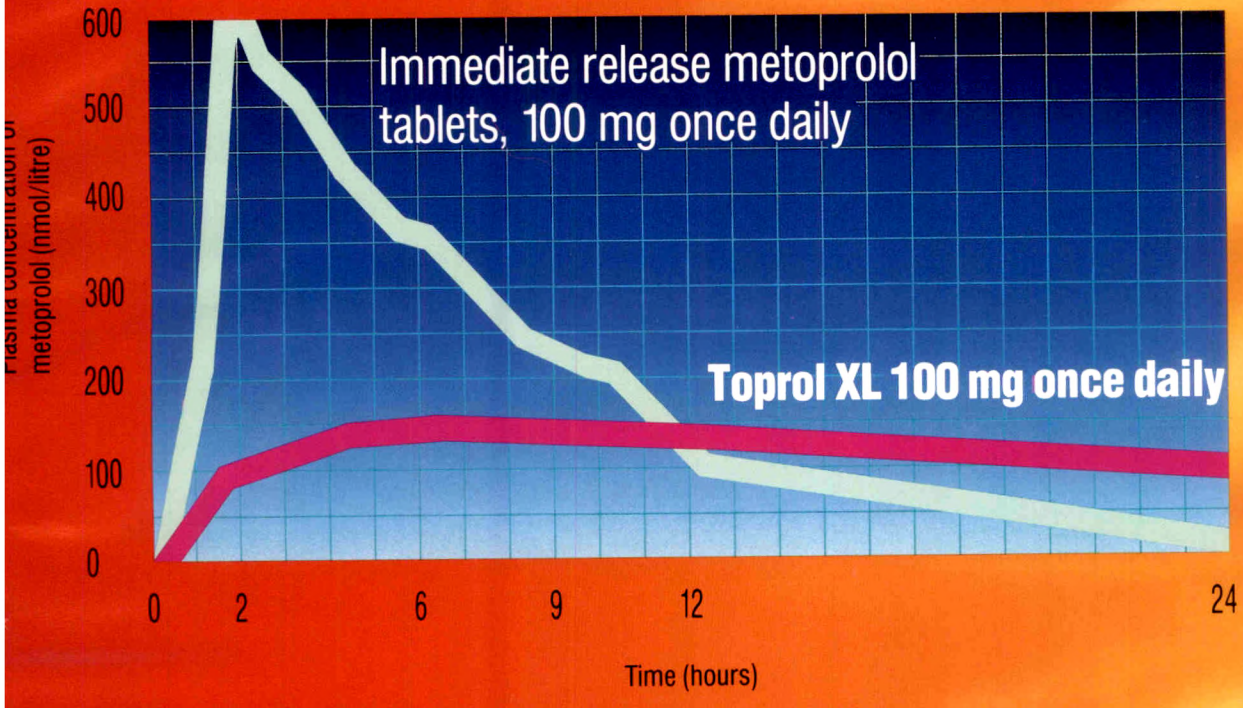
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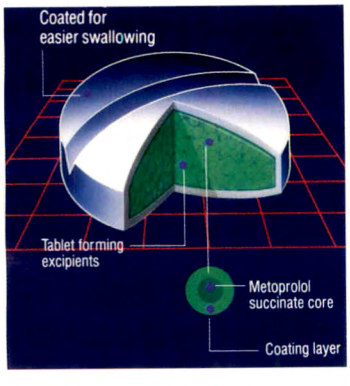
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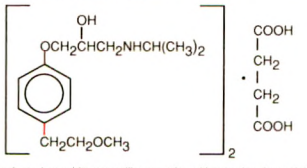
TOPROL XL™ TABLETS

(Metoprolol succinate)

Extended Release Tablets
Tablets: 50 mg, 100 mg, and 200 mg

DESCRIPTION

Toprol XL, metoprolol succinate, is a beta$_1$-selective (cardioselective) adrenoceptor blocking agent, for oral administration, available as extended release tablets. Toprol XL has been formulated to provide a controlled and predictable release of metoprolol for once daily administration. The tablets comprise a multiple unit system containing metoprolol succinate in a multitude of controlled release pellets. Each pellet acts as a separate drug delivery unit and is designed to deliver metoprolol continuously over the dosage interval. The tablets contain 47.5 mg, 95 mg and 190 mg of metoprolol succinate equivalent to 50, 100 and 200 mg of metoprolol tartrate, USP, respectively. Its chemical name is (±)1-(isopropylamino)-3-[p-(2-methoxyethyl) phenoxy]-2-propanol succinate (2:1) (salt). Its structural formula is:



Metoprolol succinate is a white crystalline powder with a molecular weight of 652.8. It is freely soluble in water; soluble in methanol; sparingly soluble in ethanol; slightly soluble in dichloromethane and 2-propanol; practically insoluble in ethyl-acetate, acetone, diethylether and heptane. Inactive ingredients: Silicone dioxide, Cellulose compounds, Acetyltributyl citrate, Maize starch, Lactose powder, Polyvidone, Magnesium stearate, Polyethylene glycol, Titanium dioxide, Paraffin.

CLINICAL PHARMACOLOGY

Metoprolol is a beta$_1$-selective (cardioselective) adrenergic receptor blocking agent. This preferential effect is not absolute, however, and at higher plasma concentrations, metoprolol also inhibits beta$_2$-adrenoreceptors, chiefly located in the bronchial and vascular musculature. Metoprolol has no intrinsic sympathomimetic activity, and membrane-stabilizing activity is detectable only at plasma concentrations much greater than required for beta-blockade. Animal and human experiments indicate that metoprolol slows the sinus rate and decreases AV nodal conduction.

Clinical pharmacology studies have confirmed the beta-blocking activity of metoprolol in man, as shown by (1) reduction in heart rate and cardiac output at rest and upon exercise, (2) reduction of systolic blood pressure upon exercise, (3) inhibition of isoproterenol-induced tachycardia, and (4) reduction of reflex orthostatic tachycardia.

The relative beta$_1$-selectivity of metoprolol has been confirmed by the following: (1) In normal subjects, metoprolol is unable to reverse the beta$_2$-mediated vasodilating effects of epinephrine. This contrasts with the effect of nonselective beta-blockers, which completely reverse the vasodilating effects of epinephrine. (2) In asthmatic patients, metoprolol reduces FEV_1 and FVC significantly less than a nonselective beta-blocker, propranolol, at equivalent beta$_1$-receptor blocking doses.

In five controlled studies in normal healthy subjects, the same daily doses of Toprol XL and immediate release metoprolol were compared in terms of the extent and duration of beta$_1$-blockade produced. Both formulations were given in a dose range equivalent to 100–400 mg of immediate release metoprolol per day. In these studies, Toprol XL was administered once a day and immediate release metoprolol was administered once to four times a day. A sixth controlled study compared the beta$_1$-blocking effects of a 50 mg daily dose of the two formulations. In each study, beta$_1$-blockade was expressed as the percent change from baseline, in exercise heart rate following standardized submaximal exercise tolerance tests at steady state. Toprol XL administered once a day, and immediate release metoprolol administered once to four times a day, provided comparable total beta$_1$-blockade over 24 hours (area under the beta$_1$-blockade versus time curve) in the dose range 100-400 mg. At a dosage of 50 mg once daily, Toprol XL produced significantly higher total beta$_1$-blockade over 24 hours than immediate release metoprolol. For Toprol XL, the percent reduction in exercise heart rate was relatively stable throughout the entire dosage interval and the level of beta$_1$-blockade increased with increasing doses from 50 to 300 mg daily. The effects at peak/trough (i.e. at 24 hours post dosing) were; 14/9, 16/10, 24/14, 27/22 and 27/20% reduction in exercise heart rate for doses of 50, 100, 200, 300 and 400 mg Toprol XL once a day, respectively. In contrast to Toprol XL immediate release metoprolol given at a dose of 50–100 mg once a day, produced a significantly larger peak effect on exercise tachycardia, but the effect was not evident at 24 hours. To match the peak to trough ratio obtained with Toprol XL over the dosing range of 200 to 400 mg, a t.i.d. to q.i.d. divided dosing regimen was required for immediate release metoprolol.

The relationship between plasma metoprolol levels and reduction in exercise heart rate is independent of the pharmaceutical formulation. Using the E_{max} model, the maximal beta$_1$-blocking effect has been estimated to produce a 28.3% reduction in exercise heart rate. Beta$_1$-blocking effects in the range of 30–80% of the maximal effect (corresponding to approximately 8–23% reduction in exercise heart rate) are expected to occur at metoprolol plasma concentrations ranging from 30–540 nmol/L. The concentration-effect curve begins reaching a plateau between 200–300 nmol/L, and higher plasma levels produce little additional beta$_1$-blocking effect. The relative beta$_1$-selectivity of metoprolol diminishes and blockade of beta$_2$-adrenoceptors increases at higher plasma concentrations.

Although beta-adrenergic receptor blockade is useful in the treatment of angina and hypertension, there are situations in which sympathetic stimulation is vital. In patients with severely damaged hearts, adequate ventricular function may depend on sympathetic drive. In the presence of AV block, beta-blockade may prevent the necessary facilitating effect of sympathetic activity on conduction. Beta$_2$-adrenergic blockade results in passive bronchial constriction by interfering with endogenous adrenergic bronchodilator activity in patients subject to bronchospasm and may also interfere with exogenous bronchodilators in such patients.

Hypertension

The mechanism of the antihypertensive effects of beta-blocking agents has not been elucidated. However, several possible mechanisms have been proposed: (1) competitive antagonism of catecholamines at peripheral (especially cardiac) adrenergic neuron sites, leading to decreased cardiac output; (2) a central effect leading to reduced sympathetic outflow to the periphery; and (3) suppression of renin activity.

In controlled clinical studies, an immediate release dosage form of metoprolol has been shown to be an effective antihypertensive agent when used alone or as concomitant therapy with thiazide-type diuretics at dosages of 100–450 mg daily. Toprol XL, in dosages of 100 to 400 mg once daily, has been shown to possess comparable β_1-blockade as conventional metoprolol tablets administered two to four times daily. In addition, Toprol XL administered at a dose of 50 mg once daily has been shown to lower blood pressure 24-hours post-dosing in placebo controlled studies. In controlled, comparative, clinical studies, immediate release metoprolol appeared comparable as an antihypertensive agent to propranolol, methyldopa, and thiazide-type diuretics, and to be effective both in supine and standing positions. Because of variable plasma levels attained with a given dose and lack of a consistent relationship of antihypertensive activity to drug plasma concentration, selection of proper dosage requires individual titration.

Angina Pectoris

By blocking catecholamine-induced increases in heart rate, in velocity and extent of myocardial contraction, and in blood pressure, metoprolol reduces the oxygen requirements of the heart at any given level of effort, thus making it useful in the long-term management of angina pectoris. However, in patients with heart failure, beta-adrenergic blockade may increase oxygen requirements by increasing left ventricular fiber length and end-diastolic pressure.

In controlled clinical trials, an immediate release formulation of metoprolol has been shown to be an effective antianginal agent, reducing the number of angina attacks and increasing exercise tolerance. The dosage used in these studies ranged from 100 to 400 mg daily. Toprol XL, in dosages of 100 to 400 mg once daily, has been shown to possess comparable β_1-blockade as conventional metoprolol tablets administered two to four times daily.

Pharmacokinetics

In man, absorption of metoprolol is rapid and complete. Plasma levels following oral administration of conventional metoprolol tablets, however, approximate 50% of levels following intravenous administration, indicating about 50% first-pass metabolism. Metoprolol crosses the blood-brain barrier and has been reported in the CSF in a concentration 78% of the simultaneous plasma concentration.

Plasma levels achieved are highly variable after oral administration. Only a small fraction of the drug (about 12%) is bound to human serum albumin. Elimination is mainly by biotransformation in the liver, and the plasma half-life ranges from approximately 3 to 7 hours. Less than 5% of an oral dose of metoprolol is recovered unchanged in the urine; the rest is excreted by the kidneys as metabolites that appear to have no clinical significance. Following intravenous administration of metoprolol, the urinary recovery of unchanged drug is approximately 10%. The systemic availability and half-life of metoprolol in patients with renal failure do not differ to a clinically significant degree from those in normal subjects. Consequently, no reduction in dosage is usually needed in patients with chronic renal failure.

In comparison to conventional metoprolol, the plasma metoprolol levels following administration of Toprol XL are characterized by lower peaks, longer time to peak and significantly lower peak to trough variation. The peak plasma levels following once daily administration of Toprol XL average one-fourth to one-half the peak plasma levels obtained following a corresponding dose of conventional metoprolol, administered once daily or in divided doses. At steady state the average bioavailability of metoprolol following administration of Toprol XL, across the dosage range of 50 to 400 mg once daily, was 77% relative to the corresponding single or divided doses of conventional metoprolol. Nevertheless, over the 24 hour dosing interval, β_1-blockade is comparable and dose-related (see CLINICAL PHARMACOLOGY). The bioavailability of metoprolol shows a dose-related, although not directly proportional increase with dose and is not significantly affected by food following Toprol XL administration.

INDICATIONS AND USAGE

Hypertension

Toprol XL tablets are indicated for the treatment of hypertension. They may be used alone or in combination with other antihypertensive agents.

Angina Pectoris

Toprol XL tablets are indicated in the long-term treatment of angina pectoris.

CONTRAINDICATIONS

Hypertension and Angina

Toprol XL is contraindicated in sinus bradycardia, heart block greater than first degree, cardiogenic shock, and overt cardiac failure (see WARNINGS).

WARNINGS

Hypertension and Angina

Cardiac Failure: Sympathetic stimulation is a vital component supporting circulatory function in congestive heart failure, and beta-blockade carries the potential hazard of further depressing myocardial contractility and precipitating more severe failure. In hypertensive and angina patients who have congestive heart failure controlled by digitalis and diuretics, Toprol XL should be administered cautiously. Both digitalis and Toprol XL slow AV conduction.

In Patients Without a History of Cardiac Failure: Continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or given a diuretic. The response should be observed closely. If cardiac failure continues, despite adequate digitalization and diuretic therapy, Toprol XL should be withdrawn.

Ischemic Heart Disease: Following abrupt cessation of therapy with certain beta-blocking agents, exacerbations of angina pectoris and, in some cases, myocardial infarction have occurred. When discontinuing chronically administered Toprol XL, particularly in patients with ischemic heart disease, the dosage should be gradually reduced over a period of 1–2 weeks and the patient should be carefully monitored. If angina markedly worsens or acute coronary insufficiency develops, Toprol XL administration should be reinstated promptly, at least temporarily, and other measures appropriate for the management of unstable angina should be taken. Patients should be warned against interruption or discontinuation of therapy without the physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue Toprol XL therapy abruptly even in patients treated only for hypertension.

Bronchospastic Diseases: PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD, IN GENERAL, NOT RECEIVE BETA-BLOCKERS. Because of its relative beta$_1$-selectivity, however, Toprol XL may be used with caution in patients with bronchospastic disease who do not respond to, or cannot tolerate, other antihypertensive treatment. Since beta$_1$-selectivity is not absolute, a beta$_2$-stimulating agent should be administered concomitantly, and the lowest possible dose of Toprol XL should be used (see DOSAGE AND ADMINISTRATION).

Major Surgery: The necessity or desirability of withdrawing beta-blocking therapy prior to major surgery is controversial; the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures.

Toprol XL like other beta-blockers, is a competitive inhibitor of beta-receptor agonists, and its effects can be reversed by administration of such agents, e.g., dobutamine or isoproterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in restarting and maintaining the heart beat has also been reported with beta-blockers.

Diabetes and Hypoglycemia: Toprol XL should be used with caution in diabetic patients if a beta-blocking agent is required. Beta-blockers may mask tachycardia occurring with hypoglycemia, but other manifestations such as dizziness and sweating may not be significantly affected.

Thyrotoxicosis: Beta-adrenergic blockade may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. Patients suspected of developing thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of beta-blockade, which might precipitate a thyroid storm.

PRECAUTIONS

General

Toprol XL should be used with caution in patients with impaired hepatic function.

Information for Patients

Patients should be advised to take Toprol XL regularly and continuously, as directed, preferably with or immediately following meals. If a dose should be missed, the patient should take only the next scheduled dose (without doubling it). Patients should not discontinue Toprol XL without consulting the physician.

Patients should be advised (1) to avoid operating automobiles and machinery or engaging in other tasks requiring alertness until the patient's response to therapy with Toprol XL has been determined; (2) to contact the physician if any difficulty in breathing occurs; (3) to inform the physician or dentist before any type of surgery that he or she is taking Toprol XL.

Laboratory Tests

Clinical laboratory findings may include elevated levels of serum transaminase, alkaline phosphatase, and lactate dehydrogenase.

Drug Interactions

Catecholamine-depleting drugs (e.g., reserpine) may have an additive effect when given with beta-blocking agents. Patients treated with Toprol XL plus a catecholamine depletor should therefore be closely observed for evidence of hypotension or marked bradycardia, which may produce vertigo, syncope, or postural hypotension.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies in animals have been conducted to evaluate the carcinogenic potential of metoprolol tartrate. In 2-year studies in rats at three oral dosage levels of up to 800 mg/kg/day, there was no increase in the development of spontaneously occurring benign or malignant neoplasms of any type. The only histologic changes that appeared to be drug related were an increased incidence of generally mild focal accumulation of foamy macrophages in pulmonary alveoli and a slight increase in biliary hyperplasia. In a 21-month study in Swiss albino mice at three oral dosage levels of up to 750 mg/kg/day, benign lung tumors (small adenomas) occurred more frequently in female mice receiving the highest dose than in untreated control animals. There was no increase in malignant or total (benign plus malignant) lung tumors, nor in the overall incidence of tumors or malignant tumors. This 21-month study was repeated in CD-1 mice, and no statistically or biologically significant differences were observed between treated and control mice of either sex for any type of tumor.

All mutagenicity tests performed on metoprolol tartrate (a dominant lethal study in mice, chromosome studies in somatic cells, a Salmonella/mammalian-microsome mutagenicity test, and a nucleus anomaly test in somatic interphase nuclei) and metoprolol succinate (a Salmonella/mammalian-microsome mutagenicity test) were negative.

No evidence of impaired fertility due to metoprolol tartrate was observed in a study performed in rats at doses up to 55.5 times the maximum daily human dose of 450 mg.

Pregnancy Category C

Metoprolol tartrate has been shown to increase post-implantation loss and decrease neonatal survival in rats at doses up to 55.5 times the maximum daily human dose of 450 mg. Distribution studies in mice confirm exposure of the fetus when metoprolol tartrate is administered to the pregnant animal. These studies have revealed no evidence of impaired fertility or teratogenicity. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers

Metoprolol is excreted in breast milk in very small quantities. An infant consuming 1 liter of breast milk daily would receive a dose of less than 1 mg of the drug. Caution should be exercised when Toprol XL is administered to a nursing woman.

Pediatric Use

Safety and effectiveness in children have not been established.

Risk Of Anaphylactic Reactions

While taking beta-blockers, patients with a history of severe anaphylactic reactions to a variety of allergens may be more reactive to repeated challenge, either accidental, diagnostic or therapeutic. Such patients may be unresponsive to the usual doses of epinephrine used to treat allergic reaction.

ADVERSE REACTIONS

Hypertension and Angina

Most adverse effects have been mild and transient. The following adverse reactions have been reported for metoprolol tartrate.

Central Nervous System: Tiredness and dizziness have occurred in about 10 of 100 patients. Depression has been reported in about 5 of 100 patients. Mental confusion and short-term memory loss have been reported. Headache, somnolence, nightmares, and insomnia have also been reported.

Cardiovascular: Shortness of breath and bradycardia have occurred in approximately 3 of 100 patients. Cold extremities; arterial insufficiency, usually of the Raynaud type; palpitations; congestive heart failure; peripheral edema; syncope; chest pain; and hypotension have been reported in about 1 of 100 patients (see CONTRAINDICATIONS, WARNINGS and PRECAUTIONS).

Respiratory: Wheezing (bronchospasm) and dyspnea have been reported in about 1 of 100 patients (see WARNINGS).

Gastrointestinal: Diarrhea has occurred in about 5 of 100 patients. Nausea, dry mouth, gastric pain, constipation, flatulence, digestive tract disorders and heartburn have been reported in about 1 of 100 patients.

Hypersensitive Reactions: Pruritus or rash have occurred in about 5 of 100 patients. Worsening of psoriasis has also been reported.

Miscellaneous: Peyronie's disease has been reported in fewer than 1 of 100,000 patients. Musculoskeletal pain, blurred vision, decreased libido and tinnitus have also been reported.

There have been rare reports of reversible alopecia, agranulocytosis, and dry eyes. Discontinuation of the drug should be considered if any such reaction is not otherwise explicable. The oculomucocutaneous syndrome associated with the beta-blocker practolol has not been reported with metoprolol.

Potential Adverse Reactions

A variety of adverse reactions not listed above have been reported with other beta-adrenergic blocking agents and should be considered potential adverse reactions to Toprol XL.

Central Nervous System: Reversible mental depression progressing to catatonia; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.

Cardiovascular: Intensification of AV block (see CONTRAINDICATIONS).

Hematologic: Agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

Hypersensitive Reactions: Fever combined with aching and sore throat, laryngospasm, and respiratory distress.

OVERDOSAGE

Acute Toxicity

No overdosage has been reported with Toprol XL and no specific overdosage information was obtained with this drug, with the exception of animal toxicology data. However, since Toprol XL (metoprolol succinate salt) contains the same active moiety, metoprolol, as conventional metoprolol tablets (metoprolol tartrate salt), the recommendations on overdosage for metoprolol conventional tablets are applicable to Toprol XL.

Signs and Symptoms

Potential signs and symptoms associated with overdosage with metoprolol are bradycardia, hypotension, bronchospasm, and cardiac failure.

Treatment

There is no specific antidote.

In general, patients with acute or recent myocardial infarction may be more hemodynamically unstable than other patients and should be treated accordingly. On the basis of the pharmacologic actions of metoprolol tartrate, the following general measures should be employed.

Elimination of the Drug: Gastric lavage should be performed.

Bradycardia: Atropine should be administered. If there is no response to vagal blockade, isoproterenol should be administered cautiously.

Hypotension: A vasopressor should be administered, e.g., levarterenol or dopamine.

Bronchospasm: A beta$_2$-stimulating agent and/or a theophylline derivative should be administered.

Cardiac Failure: A digitalis glycoside and diuretics should be administered. In shock resulting from inadequate cardiac contractility, administration of dobutamine, isoproterenol or glucagon may be considered.

DOSAGE AND ADMINISTRATION

Toprol XL is an extended release tablet intended for once-a-day administration. When switching from immediate release metoprolol tablet to Toprol XL, the same total daily dose of Toprol XL should be used.

As with immediate release metoprolol, dosages of Toprol XL should be individualized and titration may be needed in some patients.

Hypertension

The usual initial dosage is 50 to 100 mg daily in a single dose, whether used alone or added to a diuretic. The dosage may be increased at weekly (or longer) intervals until optimum blood pressure reduction is achieved. In general, the maximum effect of any given dosage level will be apparent after 1 week of therapy. Dosages above 400 mg per day have not been studied.

Angina Pectoris

The dosage of Toprol XL should be individualized. The usual initial dosage is 100 mg daily, given in a single dose. The dosage may be gradually increased at weekly intervals until optimum clinical response has been obtained or there is a pronounced slowing of the heart rate. Dosages above 400 mg per day have not been studied. If treatment is to be discontinued, the dosage should be reduced gradually over a period of 1-2 weeks (see WARNINGS).

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1. Please see full prescribing information above.
2. Sandberg A, Blomqvist I, Jonsson UE, Lundborg P, Pharmacokinetic and pharmacodynamic properties of a new controlled-release formulation of metoprolol; a comparison with conventional tablets. Eur J Clin Pharmacol 1988; 33 (Suppl); S9-S14.
3. Data on file at AB Hassle.

Usefulness of Pirenzepine, an M_1 Antimuscarinic Agent, for Effort Myocardial Ischemia

Paolo Marraccini, MD, Enrico Orsini, MD, Guido Nassi, Claudio Michelassi, and Antonio L'Abbate, MD

This study evaluated the effect of pirenzepine, an M_1 antimuscarinic agent, on exercise duration and ischemic threshold in patients with angiographically documented coronary artery disease and clear-cut ST depression (>0.2 mV, 0.08 second after the J point) during ergometric stress testing. Twenty-five patients, mean age 56 ± 8 years, underwent 3 randomized multistage bicycle exercise stress tests after intravenous administration of saline solution (2 ml), isosorbide dinitrate (1 mg) and pirenzepine (2 mg). Isosorbide dinitrate, an endothelium-independent coronary dilating agent, was used as a reference drug. Compared with saline, both pirenzepine and isosorbide dinitrate significantly improved time to ischemia (0.15 mV ST-segment depression) from 6.5 ± 2 to 7.8 ± 2 and 8.6 ± 2 minutes and rate-pressure product at ischemia from 21,498 ± 4,903 to 24,083 ± 6,692 and 24,547 ± 5,390 mm Hg · beats/min, respectively. Compared with saline, pirenzepine did not induce significant changes in blood pressure either at rest or during exercise, whereas it decreased resting heart rate from 71 ± 9 to 60 ± 11 beats/min ($p < 0.01$) and induced a significant increment of heart rate during ischemia from 117 ± 18 to 126 ± 21 beats/min ($p < 0.05$). Compared with saline, isosorbide dinitrate reduced systolic blood pressure at rest from 132 ± 12 to 112 ± 12 mm Hg, increased heart rate at rest from 71 ± 10 to 84 ± 16 beats/min and heart rate at ischemia from 117 ± 18 to 132 ± 16 beats/min.

These results suggest that pirenzepine can improve exercise tolerance in patients with effort ischemia; if the results of this study were to be confirmed, the M_1 antimuscarinic agents could be considered as a new alternative treatment of effort myocardial ischemia.

(Am J Cardiol 1992;69:1407–1411)

The importance of the coronary vasomotor tone in modulating myocardial blood flow is well established.[1] Several factors, such as blood cell products, endothelium-derived vasoactive substances, hormones, growth factors, neuropeptides and physicochemical stimuli can affect vascular tone. Most of these stimuli display an indirect endothelium-dependent vasodilator activity as well as a direct constrictor effect.[2] The intracellular signal transduction is mediated by a second messenger, such as guanosine and adenosine monophosphate systems, which in turn is modulated through the G-protein system by the activity of muscarinic and sympathetic receptors.[3] In the presence of endothelial damage, caused by coronary atherosclerosis, the balance between dilator and constrictor stimuli can be impaired.[4] In the case of stimuli mediated by guanosine monophosphate system it could be hypothesized that the activity of M_3 coronary muscarinic receptors[5] might facilitate the direct constrictor effect on smooth vascular muscles. This hypothesis is supported by the observation of Busse et al,[6] who refer to the vasoactive effect of adventitial application of acetylcholine in peripheral and coronary arteries, and by a recent clinical report[7] describing an improvement in the ischemic threshold in patients with effort ischemia after intravenous administration of atropine. In this study we report the effects of intravenous administration of pirenzepine, an M_1 antimuscarinic agent both at rest and during exercise in patients with effort-induced ischemia. The interest for pirenzepine was due to its opposite effect on M_2 atrial receptors and M_3 smooth muscle receptors. In particular, selective M_1 blockade in normal subjects increases M_2 activity, reducing sinus node rate,[8] and decreases M_3 activity, reducing intestinal smooth muscle tone.[3]

METHODS

Patients: Candidates for this study were patients with a history of effort angina of unchanged severity in the last 3 months, clear-cut ST-segment depression during exercise stress testing (>0.2 mV, 0.08 second after the J point) and angiographically documented coronary artery disease. Patients with associate pathologic conditions that could have interfered with the interpretation of ST shift were carefully excluded.

Of 28 consecutive patients, 25 gave their informed consent and took part in the study. Clinical and angiographic characteristics of these patients are listed in Table I.

Study protocol: All patients performed 3 exercise stress tests on 3 consecutive days following a pharmacologic washout of ≥72 hours, during which only short-

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TABLE I Clinical Features

Pt.	Age (yr) & Sex	Healed MI	SH	No. of CAs	Coronary Stenosis (% DR)						CC	LVEF (%)
					LAD	D	LC	M	Right	LM		
1	61M	0	0	2	75	90	—	—	75	—	0	52
2	44M	0	0	1	90	—	—	—	—	—	0	72
3	43M	0	0	3	90	75	100	75	50	—	+	68
4	59M	Lateral	0	2	—	—	90	90	75	—	0	44
5	58M	0	0	2	100	75	—	—	90	—	+	72
6	47M	Inferior	0	1	—	75	—	—	100	—	+	57
7	44M	0	0	3	50	90	75	—	50	—	0	71
8	50M	Inferior	0	2	—	75	50	—	100	—	+	49
9	65M	Inferior	+	3	75	90	75	75	90	—	+	67
10	56M	0	0	1	90	—	—	—	—	—	0	64
11	61M	Anterior	0	3	100	100	75	—	100	—	+	55
12	66M	Inferior	+	1	—	—	—	—	90	—	0	45
13	69M	0	0	3	75	—	90	—	75	90	0	—
14	53M	0	0	1	—	90	—	—	50	—	0	63
15	60F	0	0	2	75	100	—	—	90	—	+	67
16	43M	Inferior	+	3	100	75	100	75	100	—	+	55
17	57M	Apical	0	2	100	—	75	—	—	—	0	37
18	51M	0	0	1	—	100	75	—	—	—	+	55
19	67M	Lateral	0	3	90	—	90	—	75	75	+	69
20	63M	Inferior	0	2	90	75	—	—	100	—	+	47
21	54M	Anterior	0	2	90	—	100	—	—	—	+	60
22	60M	0	0	1	75	—	—	100	—	—	0	60
23	55M	Anterior	0	3	90	—	50	—	50	—	0	60
24	57M	Inferior	0	1	—	—	100	—	—	—	+	48
25	57M	0	0	2	90	90	—	75	50	—	+	65

CAs = coronary arteries narrowed >50% in diameter; CC = collateral circulation; D = diagonal branch; DR = diameter reduction; LAD = left anterior descending artery; LC = left circumflex artery; LM = left main; LVEF = left ventricular ejection fraction; M = marginal branch; MI = myocardial infarction; SH = systemic hypertension; + = positive; − = negative.

acting nitrates were allowed if needed. The tests were performed in a randomized sequence after intravenous administration of saline (2 ml), pirenzepine (2 mg) and isosorbide dinitrate (1 mg).

Exercise stress test: Tests were always performed in the morning and ≥3 hours after the intake of sublingual nitrates, when appropriate. Patients exercised on an electromagnetic bicycle with load increments of 25 W every 2 minutes. A 12-lead electrocardiogram and blood pressure (cuff sphygmomanometer) were recorded at baseline and every minute during exercise and in the recovery phase (≥5 minutes up to the normalization of the electrocardiogram); 3 electrocardiographic leads were continuously monitored throughout the test. Criteria for test interruption were clear-cut ischemic ST-segment depression (>0.2 mV) with or without anginal pain, significant decrease in systolic blood pressure, severe dyspnea, troublesome ventricular arrhythmias, maximal age-related heart rate and muscular exhaustion. Tests were begun 5 minutes after intravenous drug administration. Analysis of ST-segment trends was retrospectively, independently and blindly performed by 2 of us. We had to identify both the time of onset of ischemia, defined as the time corresponding to ST depression of 0.15 mV 0.08 second after the J point, and the maximal ST-segment shift. Agreement was found in 96% of the tests.

The following parameters were considered for analysis: time to onset of ischemia, heart rate, systolic blood pressure, and rate-pressure product at rest, at the onset of ischemia and at peak exercise. Linear regressions between time of exercise and the corresponding values of heart rate, systolic blood pressure and rate-pressure product were computed; the slopes of these regressions were used as descriptive of the rate of increment of hemodynamic parameters during exercise as previously described.[9] In addition, the increment in heart rate in the first minute of exercise and the increment per minute in the last 2 minutes of exercise were included in the analysis. This was done according to the observations of Maciel[10] and Robinson[11] and their co-workers who described the relative contribution of parasympathetic and sympathetic systems in heart rate control during exercise in order to obtain indirect information on parasympathetic withdrawal at the onset of exercise and on sympathetic drive in the final minutes of exercise.

Statistical analysis: Comparisons were made using analysis of variance for repeated measurements. Data were expressed as mean ± SD. A p value <0.05 was considered significant.

RESULTS (Table II)

All patients ended the study without significant complications. After intravenous administration of pirenzepine, 3 patients claimed dryness of the mouth. Isosorbide dinitrate induced transient hypotension and dizziness, which rapidly subsided with exercise in 4 patients.

Compared with saline, both pirenzepine and isosorbide dinitrate significantly ($p < 0.01$) increased exercise

TABLE II Exercise Stress Test Results

	Basal (B)	ISDN (I)	Pirenzepine (P)	Statistical Analysis B-I	B-P	I-P
Exercise duration (min)	7.2 ± 2.2	8.9 ± 1.9	8.1 ± 1.8	†	†	†
Time to 0.15 mV ST– (min)	6.5 ± 1.9	8.6 ± 1.9	7.8 ± 1.8	†	†	†
HR at rest (beats/min)	70.9 ± 9.6	83.6 ± 15.8	59.8 ± 11	†	†	†
HR increment in the first minute of exercise (beats/min)	17 ± 9.2	7.2 ± 11	19.3 ± 9.7	†		†
HR slope (beats/min per minute)	6.4 ± 2.2	5.7 ± 1.8	8 ± 2.7		†	†
HR increment per minute in the last 2 minutes of exercise (beats/min)	8 ± 4.3	9.4 ± 3.7	9.9 ± 3		*	
HR at 0.15 mV ST– (beats/min)	117.1 ± 18	131.6 ± 16.5	126.2 ± 21.5	†	*	
Max. HR (beats/min)	121.9 ± 16.6	134.8 ± 14.4	129.2 ± 20.4	†	*	
% of max. predicted HR	74.4 ± 11.2	82.3 ± 9.6	79 ± 13.7	†	*	
Systolic BP at rest (mm Hg)	132.2 ± 12	112.4 ± 12	124.6 ± 16.8	†		†
Systolic BP slope (mm Hg/min)	8 ± 2.1	8.6 ± 2.5	8.2 ± 2.9			
Systolic BP at 0.15 mV ST– (mm Hg)	182.2 ± 18.9	184.8 ± 24.2	188.4 ± 24.3			
Max. systolic BP (mm Hg)	190.2 ± 19.6	188.4 ± 23.3	191.2 ± 24.2			
RPP at rest (mm Hg · beats/min)	9,414 ± 1,791	9,416 ± 2,078	7,523 ± 2,010		†	†
RPP slope (mm Hg · beats/min per minute)	1,806 ± 511	1,786 ± 538	2,062 ± 752			
RPP at 0.15 mV ST– (mm Hg · beats/min)	21,498 ± 4,903	24,547 ± 5,390	24,083 ± 6,692	†	*	
Max. RPP (mm Hg · beats/min)	23,288 ± 4,744	25,562 ± 4,992	24,946 ± 6,525	*		
Max. ST shift (mV)	0.21 ± 0.06	0.17 ± 0.08	0.19 ± 0.08	†		

*p ≤0.05; †p ≤0.01.
Basal = baseline test; BP = blood pressure; HR = heart rate; ISDN = isosorbide dinitrate; Max. = maximal; RPP = rate-pressure product; ST– = ST = segment depression.

time to ischemia from 6.5 ± 1.9 to 7.8 ± 1.8 and 8.6 ± 1.9 minutes, respectively. However, the improvement with isosorbide dinitrate was much greater than that with pirenzepine ($p < 0.01$).

Hemodynamic effects of pirenzepine: Compared with saline, pirenzepine at rest induced a decrease in heart rate from 71 ± 10 to 60 ± 11 beats/min ($p < 0.01$), without affecting the atrioventricular conduction (PR interval) and without significant changes in systolic pressure. Thus, resting rate-pressure product significantly decreased from 9,414 ± 1,791 to 7,523 ± 2,011 mm Hg · beats/min ($p < 0.01$). Moreover, compared with the control test, pirenzepine significantly increased heart rate at ischemia (126 ± 21 vs 117 ± 18 beats/min, $p < 0.05$) and rate-pressure product at ischemia (24,083 ± 6,692 vs 21,498 ± 4,903 mm Hg · beats/min, $p < 0.05$; Figure 1), without changes in systolic blood pressure. During exercise, the slope of the heart rate was much higher with pirenzepine than it was during the control test (8 ± 3 vs 6.4 ± 2 beats/min per minute; $p < 0.01$); the slope of rate-pressure product yielded similar results, although the difference was not significant. This behavior does not seem to be related to a greater parasympathetic withdrawal at the onset of

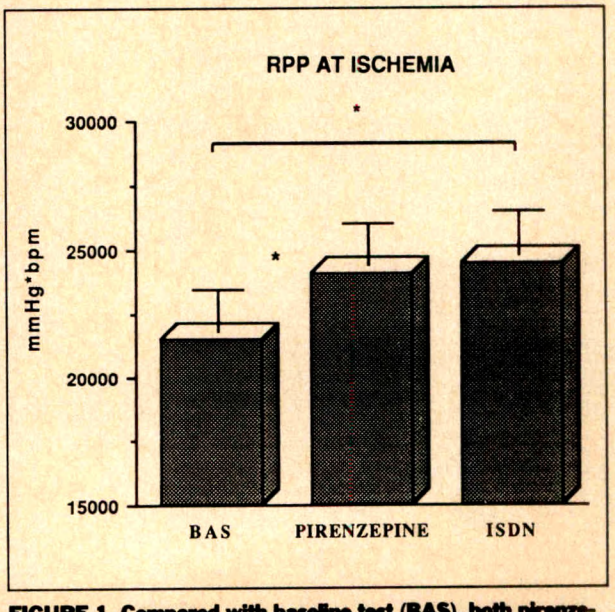


FIGURE 1. Compared with baseline test (BAS), both pirenzepine and isosorbide dinitrate (ISDN) significantly increased, and to the same extent, rate-pressure product (RPP) at ischemia.

exercise; in fact, the increment of heart rate in the first minute of exercise with pirenzepine was similar to heart rate in control tests. It could be explained by the steeper increment per minute of heart rate in the last 2 minutes of exercise, an indirect index of sympathetic drive.

Hemodynamic effects of isosorbide dinitrate: Compared with saline, the intravenous administration of 1 mg of isosorbide dinitrate induced a reduction in resting systolic pressure and an increase in heart rate with no change in rate-pressure product. The slope of heart rate during exercise decreased significantly (5.7 ± 2 vs 6.4 ± 2 beats/min per minute; $p < 0.05$), probably due to the influence of the resting relative tachycardia; however, the slope of rate-pressure product was not statistically different from control. Moreover, isosorbide dinitrate significantly increased heart rate at ischemia (132 ± 16 vs 117 ± 18 beats/min, $p < 0.01$) and rate-pressure product at ischemia (24,547 ± 5,390 vs 21,498 ± 4,903 mm Hg · beats/min, $p < 0.01$) (Figure 1).

DISCUSSION

The results of this study suggest that pirenzepine, a peripheral M_1 antimuscarinic agent,[3] is effective in the treatment of exercise-induced myocardial ischemia. This therapeutic effect seems to be related to 2 different mechanisms: a reduction in resting rate-pressure product and an increment in rate-pressure product at ischemia (Figure 2, Table II). The improvement of ischemic threshold (rate-pressure product at ischemia) obtained with pirenzepine was similar to that obtained with isosorbide dinitrate (Figure 1, Table II). This result, already reported for atropine,[7] seems to confirm the hypothesis of a parasympathetic regulation of coronary circulation. M_3 muscarinic receptors have been documented in the media of coronary arteries.[5] Both the molecular structure and function of these receptors are very similar to M_3 muscarinic receptors of the gastrointestinal smooth muscle. In the intestine, M_1 muscarinic blockade controls the discharge of M_3 receptors reduc-

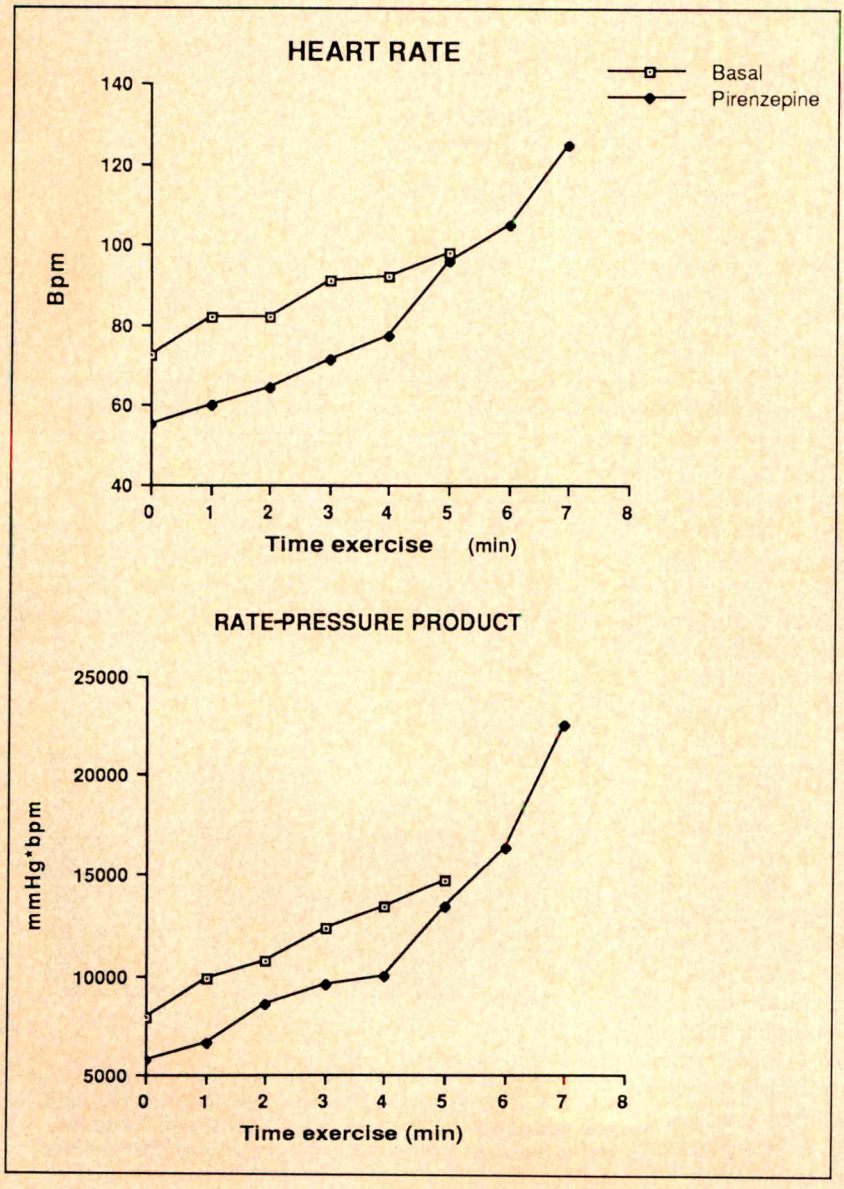


FIGURE 2. Effect in 1 patient of intravenous administration of pirenzepine on heart rate *(upper panel)* and rate-pressure product *(lower panel)* at rest and during exercise. The time to 0.15 mV ST-segment depression was increased from 5 to 7 minutes of exercise. A relative bradycardia, which reduced rate-pressure product, was present until the fourth minute of exercise; after this period, probably in response to sympathetic drive, the slope of heart rate and rate-pressure product was steeper; the heart rate and rate-pressure product at ischemia were higher than during the control test.

ing the smooth muscle contractility; for this reason M_1 inhibitors are clinically used in the treatment of irritable bowel syndrome.[3] On the basis of these observations a vasodilator effect should be expected after M_1 blockade. However, this effect can probably be manifest only in the presence of endothelium dysfunction. In this case, the balance between dilator (production of nitric oxide) and constrictor (direct stimulation of smooth arterial muscle) signals is altered, resulting in a paradoxic vasoconstriction that could be reversed by antimuscarinic agents. The reduction of resting rate-pressure product induced by pirenzepine was related to a decrease in heart rate. This cholinomimetic effect, already documented for doses ranging between 0.01 and 0.1 mg/kg,[8] is not due to a direct effect of the drug on the sinus node, but rather to the blockade of inhibitory M_1 autoreceptors that interrupts a negative auto feedback mechanism.[12] However, relative bradycardia is maintained during mild levels of exercise (Figure 2), whereas at higher levels the heart rate increases, probably in response to the sympathetic drive that overcomes the cholinomimetic effect.

In conclusion, M_1 blockers may represent a new class of anti-ischemic drugs. More detailed studies are needed to characterize the effects of these drugs on sinus node activity, myocardial contractility and coronary circulation. In addition, blind and controlled trials may be necessary to confirm the anti-ischemic activity of pirenzepine and to investigate the possible efficacy and pharmacokinetics of oral administration.

Acknowledgment: We wish to thank our colleagues of the Coronary Research Group of the CNR Institute of Clinical Physiology for their collaboration and constructive criticisms, all the nursing staff and, in particular, Desolina Vargiu for her daily assistance in the ergometer laboratory.

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Simultaneous Transesophageal Two-Dimensional Echocardiography and Atrial Pacing for Detecting Coronary Artery Disease

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This study describes a new technique for assessing wall motion abnormalities, combining transesophageal echocardiography (TEE) and transesophageal atrial pacing in 71 patients. Stable capture was reached in 70 patients (99%). In 3 patients (4%) pacing was discontinued prematurely because of discomfort. TEE during pacing was performed in 52 patients with and in 18 patients without coronary artery disease (CAD). In 43 of 52 patients with CAD, regional wall motion abnormalities occurred (sensitivity 83%). No wall motion abnormalities occurred in 17 of 18 patients without CAD (specificity 94%, positive predictive value 98%). Wall motion abnormalities related to another vascular region were observed in 17 of 22 patients with previous myocardial infarction (sensitivity 77%, specificity 100%, positive predictive value 100%). Simultaneous 12-lead electrocardiography during atrial pacing was performed in 57 patients and yielded positive results in 21 of 40 patients with (sensitivity 52%) and in 3 of 17 patients without (specificity 82%, positive predictive value 88%) CAD.

Exercise stress testing was performed in 66 patients. Twenty-four of 48 patients with CAD had a positive exercise electrocardiogram (sensitivity 50%); a false-positive exercise electrocardiogram was observed in 3 of 18 patients (specificity 83%, positive predictive value 89%). It is concluded that TEE during transesophageal atrial pacing is a feasible and promising alternative technique for the assessment of CAD, with a higher sensitivity than simultaneous 12-lead and exercise electrocardiography.

(Am J Cardiol 1992;69:1412–1416)

Detection of inducable wall motion abnormalities by transthoracic 2-dimensional echocardiography during exercise is limited because of inadequate imaging at rest or during exercise[1–5] and in patients unable to perform leg exercise. Echocardiography during atrial pacing may offer images of superior quality compared with traditional exercise echocardiography.[6–8] Transesophageal atrial pacing, with a single pacing lead, and transthoracic echocardiography cannot be performed in all patients because of failure to achieve atrial capture, or because of patient's intolerance.[7] Furthermore, poor or inadequate transthoracic imaging at rest remains a minor limitation for this technique.[6–8] Transesophageal echocardiography (TEE) provides high-resolution short-axis visualization of the left ventricle with good image quality and permits assessment and localization of regional left ventricular asynergy.[9,10] This technique can be applied for intraoperative and postoperative monitoring of new or worsened left ventricular regional wall motion abnormalities[9,10] as an early sign of myocardial ischemia.[11,12] We report the initial data of a new transesophageal device, using the combination of transesophageal 2-dimensional echocardiographic monitoring and transesophageal atrial pacing as an alternative echocardiographic stress test for the assessment of coronary artery disease (CAD). The present study was undertaken to determine the value and limitations of simultaneous transesophageal imaging and atrial pacing, and to relate these findings to coronary angiographic and electrocardiographic data.

METHODS

Patient group: The study group consisted of 71 consecutive patients studied between April 1990 and March 1991. All patients were selected for the study after informed consent had been given, and were referred to our catheterization laboratory for cardiac catheterization because of chest pain considered to be due to angina pectoris. One patient (1%) was excluded because of failure of atrial capture. Thus, 70 patients (46 men and 24 women, aged 32 to 75 years [mean 56]) were studied (Table I).

Previous myocardial infarction was present in 26 patients. CAD of at least 1 major coronary vessel with a >50% diameter stenosis was present in 52 and absent in 18 patients (Table I).

Electrocardiography: A symptom-limited treadmill exercise test according to the Bruce protocol[13] was performed 2 days before the transesophageal study in 66 patients. Four patients could not perform the exercise test because of severe claudication (n = 2), dyspnea

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(n = 1) and severe arthrosis (n = 1). A 12-lead electrocardiogram was recorded at 1-minute intervals until 5 minutes after recovery. Twenty of 26 patients myocardial infarction had an abnormal electrocardiogram at rest (Q-wave infarction); all other patients had a normal electrocardiogram at rest.

During atrial pacing a 12-lead electrocardiogram was obtained in 57 of the 70 patients (excluding the first 13 patients of this study). Each patient was continuously monitored before, during and 2 minutes after the test.

ST-segment depression (treadmill and atrial pacing) was measured in millivolts at 80 ms after the J point. Ischemia was diagnosed if a new horizontal or downsloping ST-segment depression of ≥0.1mV occurred in ≥3 consecutive complexes.

Transesophageal echocardiography: A commercially available 5.0 MHz transesophageal transducer mounted on the tip of a gastroscope was connected with a Hewlett-Packard 77020AC ultrasonograph. All patients fasted for ≥4 hours. Premedication was not given and a local anaesthetic (10% lignocaine) was sprayed into the patient's hypopharynx. A transesophageal atrial pacing lead (see later) was fixed anteriorly to the gastroscope, with the 4 electrodes placed between 3 and 10 cm from the tip (Figure 1). The probe was positioned to obtain a transgastric short-axis view of the left ventricle at the level of both papillary muscles. During atrial pacing the transducer remained in the same position relative to the heart; the complete study was recorded on videotape for subsequent off-line analysis for regional wall motion abnormalities. For the purpose of analysis, the short-axis view was divided into 4 segments: anterior, inferior, septal and lateral.[14] As landmarks for this division, the anterolateral and posteromedial papillary muscle and the insertion of the right ventricular free wall to the left ventricle were used. The occurrence of new or worsened wall motion abnormalities was evaluated for each segment. A change per segment from normokinesia to hypokinesia or akinesia, or a change from hypokinesia to akinesia or dyskinesia[15] was defined as positive for significant CAD.

Transesophageal atrial pacing protocol: A quadripolar silicone endocardial pacing lead with an interelectrode distance of 15 mm (Medtronic model SP 7505) was connected anteriorly to the gastroscope. A conventional pacing device (Medtronic model 2380) was used for atrial stimulation. The pulse width was initially set at 10 ms and the current and the pulse width were adjusted until atrial capture was achieved. Capture was evaluated by continuous electrocardiographic monitoring. Pacing was initiated at 10 beats/min^{-1} above the patient's own heart rate and increased every 2 minutes by 10 beats/min^{-1}, until 150 beats/min^{-1}. The protocol was terminated when atrioventricular Wenckebach block or increasing angina occurred. After the pacing protocol had been accomplished, TEE monitoring was continued for 2 minutes. Atrial pacing was successful with the use of the 2 distal electrodes in all but 1 patient. Intravenous atropine was administered to 2 patients with early atrioventricular Wenckebach block in this study.

TABLE I Important Clinical and Angiographic Findings in 70 Patients

Age (years)	32–74 (mean 56)
Men/women	46/24
Previous MI (no. of pts.)	26
Max. pacing heart rate (beats/min)	141 ± 12
Chest pain during pacing (no. of pts.)	22
Discomfort during pacing (no. of pts.)	3
No. of coronary arteries narrowed >50% in diameter	52
1	15
2	17
3	20

MI = myocardial infarction.

Cardiac catheterization and angiography: Coronary angiography was performed in all patients using the Judkins technique. Two or more projections were obtained from each coronary artery. Significant CAD was defined as a luminal diameter narrowing of ≥50% in 1 or more major coronary arteries by 2 different observers. If there was a disagreement between the 2 observers, a third observer was asked for final consensus. Left ventricular angiography was performed with a pigtail catheter and monoplane recording in the right and left anterior oblique projections.

Statistical analysis: Analysis for regional wall motion abnormalities from the echocardiograms and ST-segment depression from the electrocardiograms were performed by 2 independent observers who were unaware of the results of the patient's other data. When there was disagreement about the results, a third observer reviewed the study and the subsequent majority judgment was binding. The chi-square test was used to compare subgroups of patients on the basis of categorical variables. A p value <0.05 was considered significant. The validity of all diagnostic procedures was expressed in terms of sensitivity, specificity, and positive and negative predictive values.[16]

RESULTS

Success of the technique: In all but 1 patient, simultaneous TEE and transesophageal atrial pacing resulted in technically adequate studies (success rate 99%). The

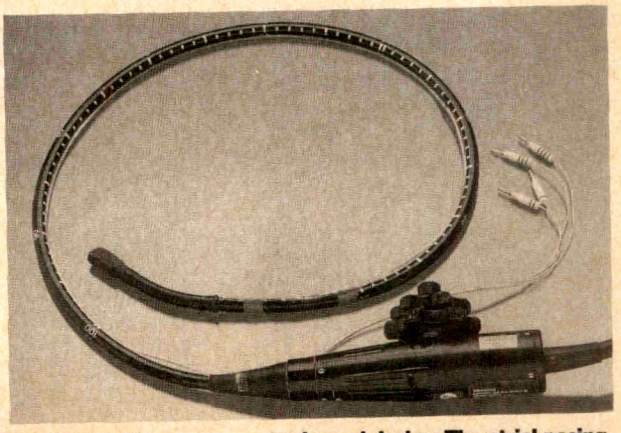


FIGURE 1. The new transesophageal device. The atrial pacing lead is connected anteriorly to the gastroscope, with the 4 ring electrodes between 3 and 10 cm from the tip.

TABLE II Sensitivity and Specificity of Transesophageal Two-Dimensional Echocardiography, 12-Lead Electrocardiography During Transesophageal Atrial Pacing, and Exercise Electrocardiography for Assessing Coronary Artery Disease

	Stress Test		
Cath.	TEE (n = 70)	12-ECG (n = 57)	X-ECG (n = 66)
CAD (n)	52	40	48
No CAD (n)	18	17	18
	WMA	ST ↓ ≥0.1 mV	ST ↓ ≥0.1 mV
Sensitivity (%)	43/52 (83)	21/40 (52)	24/48 (50)
Specificity (%)	17/18 (94)	14/17 (82)	15/18 (83)
+ pred. value (%)	43/44 (98)	21/24 (88)	24/27 (89)
− pred. value (%)	17/26 (65)	14/33 (42)	15/39 (38)

CAD = coronary artery disease; Cath. = catheterization; 12-ECG = 12-lead electrocardiography; + pred. value = positive predictive value; − pred. value = negative predictive value; ST ↓ = ST-segment depression; TEE = transesophageal echocardiography; WMA = wall motion abnormality; X-ECG = exercise electrocardiography.

TABLE III Sensitivity and Specificity of Transesophageal Two-Dimensional Echocardiography, 12-Lead Electrocardiography During Transesophageal Atrial Pacing, and Exercise Electrocardiography for Assessing Coronary Artery Disease in 57 Patients Who Underwent All Diagnostic Tests

	Stress Test		
Cath.	TEE (n = 57)	12-ECG (n = 57)	X-ECG (n = 57)
CAD (n)	40	40	40
No CAD (n)	17	17	17
	WMA	ST ≥0.1 mV	ST ≥0.1 mV
Sensitivity (%)	34/40 (85)	21/40 (52)	22/40 (55)
Specificity (%)	16/17 (94)	14/17 (82)	14/17 (82)
+ pred. value (%)	34/35 (97)	21/24 (87)	22/25 (88)
− pred. value (%)	16/22 (72)	14/33 (42)	14/32 (44)

Abbreviations as in Table II.

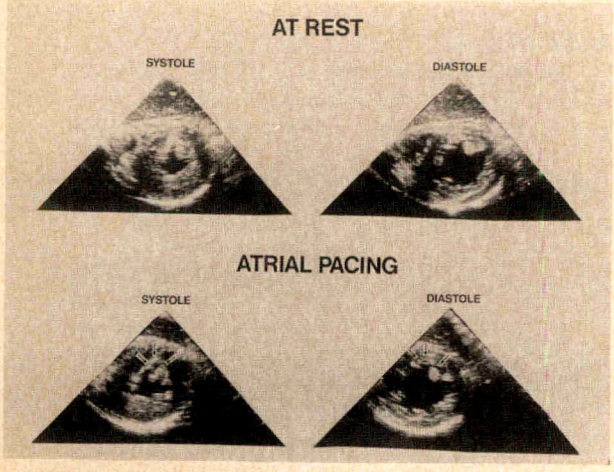


FIGURE 2. Transesophageal short-axis echocardiograms at midpapillary muscle level from a patient without myocardial infarction and the presence of 1-vessel coronary artery disease (obstruction of 70 to 90% in the dominant right coronary artery). Akinesia is observed in the inferoseptal and inferior wall *(arrows)*. End-systolic *(left)* and end-diastolic *(right)* frames at baseline *(top)* and during rapid atrial pacing *(below;* heart rate 140 beats/min) are shown.

patient with an inadequate study was excluded because of failure of atrial capture, which was related to inappropriate fixing of the atrial lead. In the remaining 70 patients, good quality echocardiographic recordings at rest and during atrial pacing were obtained in 69 patients (99%). The patient's clinical and angiographic data are summarized in Table I. Stable capture was achieved with 13 ± 3 ms pulse width of 12 ± 4 mA current strength. In 3 patients (4%), 2 with and 1 without CAD, atrial pacing had to be discontinued because of chest discomfort. In 5 patients atrioventricular Wenckeback block occurred; intravenous atropine was administered to 2 of these patients.

Electrocardiography: In 57 patients a 12-lead electrocardiogram was simultaneously recorded during transesophageal atrial pacing. Significant ST-segment depression was present in 21 of 40 patients with CAD (sensitivity 52%). In 3 of 17 patients without CAD the 12-lead electrocardiogram was false positive (specificity 82%). During atrial pacing 21 of 40 patients with CAD had ST-segment depression, whereas 34 patients had new pacing-induced wall motion abnormalities. In 66 patients a treadmill exercise 12-lead electrocardiogram was also recorded. Twenty-four of 48 patients with CAD had significant ST-segment depression (sensitivity 50%); a false-positive exercise test was found in 3 of 18 patients without CAD (specificity 83%; Table II). For purposes of comparison, the data obtained from patients in whom both a pacing electrocardiogram and an exercise electrocardiogram were performed are reported in Table III.

Transesophageal echocardiography: Simultaneous TEE and atrial pacing was performed in 70 patients. Forty-three of 52 patients with CAD developed wall motion abnormalities (sensitivity 83%); 1 patient developed dyskinesia, 28 patients developed akinesia and 14 patients hypokinesia. Each of the patients had a significant lesion in the coronary artery supplying the asynergic segment (Figure 2). Six of 9 patients with a false-negative test, defined as absence of new or worsened wall motion abnormalities during atrial pacing, had a previous myocardial infarction with extensive regional wall motion abnormalities at rest. One other patient had 1-vessel disease, with a distal stenosis of the right coronary artery, and in 2 patients atrial pacing was discontinued at a submaximal heart rate because of chest discomfort. Absence of pacing-induced wall motion abnormalities were noted in 17 of 18 patients without CAD (specificity 94%; Table II). The patient with a false-positive result had septal hypokinesia during atrial pacing. Another patient had septal hypokinesia at rest, which did not change during atrial pacing. Nineteen of the 26 patients (73%) with a previous myocardial infarction had areas of abnormal wall motion at rest, which correlated with corresponding segments of abnormal wall motion on left ventriculography. In 20 of these 26 patients (77%) new or worsened pacing-induced wall motion abnormalities were observed. One patient (4%) developed dyskinesia in the region that was hypokinetic at rest, 2 patients (8%) developed akinesia in a hypokinetic segment, 8 patients (30%) had both new pacing-induced and worsened wall motion abnormalities, 9 pa-

tients (35%) had new pacing-induced wall motion abnormalities, and 6 patients (23%) had no change in regional dysfunction. During atrial pacing, remote wall motion abnormalities (i.e., asynergy not directly adjacent to the infarcted area and supposed to be related to another major vascular region) were present in 17 of 22 patients with significant multivessel CAD (Table IV). Thus, the sensitivity of remote wall motion abnormalities in detecting multivessel CAD in patients with previous myocardial infarction was 77% by TEE and atrial pacing, whereas the sensitivity of 12-lead electrocardiography during atrial pacing and exercise electrocardiography was 45% (Table IV). TEE and atrial pacing had a sensitivity for 1-, 2- and 3-vessel disease of 69, 84 and 90%, respectively (Table V).

Variability for wall motion abnormalities: Intraobserver variability for segmental wall motion abnormalities was noted in 4 of 70 patients analyzed for a second time. In 2 patients there was disagreement about the presence of new wall motion abnormalities, and in 2 other patients about the location. Interobserver variability was noted in 6 of 70 patients; in 4 patients with regard to new wall motion abnormalities and in 2 other patients with regard to location.

Chest pain: Chest pain during atrial pacing was observed in 22 patients: 16 of 50 patients (32%) with and in 6 of 18 patients (33%) without CAD. In the 21 patients with pacing-induced wall motion abnormalities in conjunction with significant ST-segment depression, 8 patients experienced chest pain. Regional wall motion abnormalities consistently preceded ST-segment changes (with an interval of 1 to 5 minutes) and chest pain (with an interval of 2 to 8 minutes).

TABLE IV Sensitivity and Specificity of Transesophageal Two-Dimensional Echocardiography, 12-Lead Electrocardiography During Transesophageal Atrial Pacing, and Exercise Electrocardiography for Assessing Multivessel Disease After Previous Myocardial Infarction

	Stress Test		
Cath.	TEE (n = 26)	12-ECG (n = 25)*	X-ECG (n = 26)
Multivessel CAD			
Present	22	22	22
Absent	4	3	4
	Remote WMA	ST↓ ≥0.1 mV	ST↓ ≥0.1 mV
Sensitivity (%)	17/22 (77)	10/22 (45)	10/22 (45)
Specificity (%)	4/4 (100)	3/3 (100)	3/4 (75)
+ pred. value (%)	17/17 (100)	10/10 (100)	10/11 (91)
− pred. value (%)	4/9 (44)	3/15 (20)	3/15 (20)

A 12-lead electrocardiogram was not obtained in 1 patient.
Abbreviations as in Table II.

TABLE V Sensitivity of Transesophageal Two-Dimensional Echocardiography, 12-Lead Electrocardiography During Transesophageal Atrial Pacing, and Exercise Electrocardiography for Assessing One-, Two- and Three-Vessel Disease

	Sensitivity (%) of Stress Test		
Cath.	TEE (n = 52)	12-ECG (n = 40)	X-ECG (n = 48)
No. of coronary arteries narrowed >50% in diameter			
1 (%)	9/13 (69)	2/9 (22)	5/13 (38)
2 (%)	16/19 (84)	9/16 (56)	7/16 (43)
3 (%)	18/20 (90)	10/15 (66)	12/19 (63)

Abbreviations as in Table II.

DISCUSSION

In clinical practice exercise stress[17–20] testing is the established method for the diagnostic and functional assessment of patients with known or suspected CAD.

A variety of other tests for detecting CAD has been reported for patients unable to perform leg exercise. The most frequently used tests are atrial pacing and pharmacologic stress testing using dipyridamole, dobutamine or adenosine. Atrial pacing has been evaluated extensively in previous studies,[6–8,21–27] and results compare favorably with those of exercise testing for diagnosing the presence of CAD.

Exercise echocardiography has the disadvantage of poor or inadequate transthoracic images at rest in up to 15% of patients. During exercise testing only in 40 to 80% of the patients, an adequate echocardiogram is obtained due to lung interposition caused by hyperpnea and chest wall motion.[1–5,28]

Transthoracic echocardiography during transesophageal atrial pacing has been recommended as an alternative to exercise echocardiography,[6–8] because during pacing the patient breathes normally and remains immobile. Previous studies have demonstrated a high sensitivity for the assessment of CAD,[6–8] with a failure of atrial capture in up to 15%.[7] Furthermore, inadequate transthoracic echocardiographic imaging at rest was observed in 15% of the patients, although during pacing the image quality remains adequate.[6,7]

Simultaneous application of TEE and transesophageal atrial pacing appears an adequate solution for this limitation in quality of imaging at rest, and permits high-quality visualization during pacing-induced ischemia. Recently, Lambertz et al[29] reported the diagnostic use of simultaneous transesophageal atrial pacing and TEE. High diagnostic images were obtained in all patients. The technique was highly specific and sensitive for the detection of CAD.

Adequate image quality was obtained by TEE at rest and during atrial pacing in all but 1 patient in the present study. Partial dropouts of the endocardial contour in the lateral segments and gastric spasms, however, sometimes limit optimal image quality during pacing. Furthermore, in contrast to previous reports on transesophageal atrial pacing, we achieved atrial capture in 99% of our patients; an initial technical problem was the cause of failure in 1 patient. This high success rate of atrial capture can be explained by the mechanical support of the gastroscope. The anterior fixation of the pacing lead permits close contact and correct position of the stimulation electrode to the left atrium.

The improved sensitivity of this transesophageal stress technique with respect to exercise electrocardiography and 12-lead electrocardiography during pacing

can be explained by the fact that wall motion abnormalities occur earlier than ST-segment depression.[10,12] In the present study, the sensitivity and specificity of detecting multivessel CAD in patients with previous myocardial infarction was also high, and comparable with previously reported transthoracic stress echocardiography.[3]

The reason for an incomplete study in 3 patients was discomfort, probably due to muscular stimulation. Although premedication was not used, the discomfort might have been prevented by (intravenous) sedation before the procedure.

Significant ST-segment depression during 12-lead electrocardiography and pacing consistently occurred after the onset of new pacing-induced wall motion abnormalities. The same sequence has been documented in previous studies.[10,12] In addition, our findings demonstrated, that pacing-induced new or worsened wall motion abnormalities had a higher sensitivity and specificity than 12-lead electrocardiography, in keeping with these studies.

In the present study a similar incidence of chest pain in patients with and without CAD was observed, in accordance with previous data.[27] Chest pain alone appears to be nonspecific for pacing-induced ischemia.

It is conceivable that the short-axis cross section applied would be a limitation of this study because the entire left ventricle is not visualized in detail, namely the basal and apical segments. However, the sensitivity is good, indicating that pacing-induced ischemia is reflected in this cross section that comprises the watershed of all 3 major coronary arteries and appears to be the best single view to monitor regional wall motion abnormalities.[14] The recently introduced biplane probe may improve diagnostic accuracy.[30]

It is concluded that simultaneous TEE and transesophageal atrial pacing is a feasible, safe and promising new echocardiographic stress technique. Our data clearly indicate that this alternative transesophageal approach for the assessment of CAD is highly sensitive and specific. Although clinical implications need further evaluation, patients with a physical handicap or poor exercise tolerance are theoretically candidates. Furthermore, the test may be helpful in assessing the site of ischemia, and thus in selecting the ischemia-related vessel.

Acknowledgment: We wish to thank our echocardiographic technicians, Lidwien Admiraal and Sylvia Bruynzeel, for their excellent assistance, Hans Huitink for his contribution to this study, and Margreet Koelemay for preparing the manuscript.

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INDICATIONS AND USAGE
Hypertension
Lopressor tablets are indicated for the treatment of hypertension. They may be used alone or in combination with other antihypertensive agents.

Angina Pectoris
Lopressor is indicated in the long-term treatment of angina pectoris.

Myocardial Infarction
Lopressor ampuls and tablets are indicated in the treatment of hemodynamically stable patients with definite or suspected acute myocardial infarction to reduce cardiovascular mortality. Treatment with intravenous Lopressor can be initiated as soon as the patient's clinical condition allows (see **DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS,** and **WARNINGS**). Alternatively, treatment can begin within 3 to 10 days of the acute event (see **DOSAGE AND ADMINISTRATION**).

CONTRAINDICATIONS
Hypertension and Angina
Lopressor is contraindicated in sinus bradycardia, heart block greater than first degree, cardiogenic shock, and overt cardiac failure (see **WARNINGS**).

Myocardial Infarction
Lopressor is contraindicated in patients with a heart rate < 45 beats/min; second- and third-degree heart block; significant first-degree heart block (P-R interval ≥ 0.24 sec); systolic blood pressure < 100 mmHg; or moderate-to-severe cardiac failure (see **WARNINGS**).

WARNINGS
Hypertension and Angina
Cardiac Failure: Sympathetic stimulation is a vital component supporting circulatory function in congestive heart failure, and beta blockade carries the potential hazard of further depressing myocardial contractility and precipitating more severe failure. In hypertensive and angina patients who have congestive heart failure controlled by digitalis and diuretics, Lopressor should be administered cautiously. Both digitalis and Lopressor slow AV conduction.

In Patients Without a History of Cardiac Failure: Continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or given a diuretic. The response should be observed closely. If cardiac failure continues, despite adequate digitalization and diuretic therapy, Lopressor should be withdrawn.

Ischemic Heart Disease: Following abrupt cessation of therapy with certain beta-blocking agents, exacerbations of angina pectoris and, in some cases, myocardial infarction have occurred. When discontinuing chronically administered Lopressor, particularly in patients with ischemic heart disease, the dosage should be gradually reduced over a period of 1-2 weeks and the patient should be carefully monitored. If angina markedly worsens or acute coronary insufficiency develops, Lopressor administration should be reinstated promptly, at least temporarily, and other measures appropriate for the management of unstable angina should be taken. Patients should be warned against interruption or discontinuation of therapy without the physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue Lopressor therapy abruptly even in patients treated only for hypertension.

Bronchospastic Diseases: **PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD, IN GENERAL, NOT RECEIVE BETA BLOCKERS. Because of its relative beta$_1$ selectivity, however, Lopressor may be used with caution in patients with bronchospastic disease who do not respond to, or cannot tolerate, other antihypertensive treatment. Since beta$_1$ selectivity is not absolute, a beta$_2$-stimulating agent should be administered concomitantly, and the lowest possible dose of Lopressor should be used. In these circumstances it would be prudent initially to administer Lopressor in smaller doses three times daily, instead of larger doses two times daily, to avoid the higher plasma levels associated with the longer dosing interval. (See DOSAGE AND ADMINISTRATION.)**

Major Surgery: The necessity or desirability of withdrawing beta-blocking therapy prior to major surgery is controversial; the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures.

Lopressor, like other beta blockers, is a competitive inhibitor of beta-receptor agonists, and its effects can be reversed by administration of such agents, e.g., dobutamine or isoproterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in restarting and maintaining the heart beat has also been reported with beta blockers.

Diabetes and Hypoglycemia: Lopressor should be used with caution in diabetic patients if a beta-blocking agent is required. Beta blockers may mask tachycardia occurring with hypoglycemia, but other manifestations such as dizziness and sweating may not be significantly affected.

Thyrotoxicosis: Beta-adrenergic blockade may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. Patients suspected of developing thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of beta blockade, which might precipitate a thyroid storm.

Myocardial Infarction
Cardiac Failure: Sympathetic stimulation is a vital component supporting circulatory function, and beta blockade carries the potential hazard of depressing myocardial contractility and precipitating or exacerbating minimal cardiac failure.

During treatment with Lopressor, the hemodynamic status of the patient should be carefully monitored. If heart failure occurs or persists despite appropriate treatment, Lopressor should be discontinued.

Bradycardia: Lopressor produces a decrease in sinus heart rate in most patients; this decrease is greatest among patients with high initial heart rates and least among patients with low initial heart rates. Acute myocardial infarction (particularly inferior infarction) may in itself produce significant lowering of the sinus rate. If the sinus rate decreases to < 40 beats/min, particularly if associated with evidence of lowered cardiac output, atropine (0.25-0.5 mg) should be administered intravenously. If treatment with atropine is not successful, Lopressor should be discontinued, and cautious administration of isoproterenol or installation of a cardiac pacemaker should be considered.

AV Block: Lopressor slows AV conduction and may produce significant first- (P-R interval ≥0.26 sec), second-, or third-degree heart block. Acute myocardial infarction also produces heart block.

If heart block occurs, Lopressor should be discontinued and atropine (0.25-0.5 mg) should be administered intravenously. If treatment with atropine is not successful, cautious administration of isoproterenol or installation of a cardiac pacemaker should be considered.

Hypotension: If hypotension (systolic blood pressure ≤ 90 mmHg) occurs, Lopressor should be discontinued, and the hemodynamic status of the patient and the extent of myocardial damage carefully assessed. Invasive monitoring of central venous, pulmonary capillary wedge, and arterial pressures may be required. Appropriate therapy with fluids, positive inotropic agents, balloon counterpulsation, or other treatment modalities should be instituted. If hypotension is associated with sinus bradycardia or AV block, treatment should be directed at reversing these (see above).

Bronchospastic Diseases: **PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD, IN GENERAL, NOT RECEIVE BETA BLOCKERS. Because of its relative beta$_1$ selectivity, Lopressor may be used with extreme caution in patients with bronchospastic disease. Because it is unknown to what extent beta$_2$-stimulating agents may exacerbate myocardial ischemia and the extent of infarction, these agents should *not* be used prophylactically. If bronchospasm not related to congestive heart failure occurs, Lopressor should be discontinued. A theophylline derivative or a beta$_2$ agonist may be administered cautiously, depending on the clinical condition of the patient. Both theophylline derivatives and beta$_2$ agonists may produce serious cardiac arrhythmias.**

PRECAUTIONS
General
Lopressor should be used with caution in patients with impaired hepatic function.

Information for Patients
Patients should be advised to take Lopressor regularly and continuously, as directed, with or immediately following meals. If a dose should be missed, the patient should take only the next scheduled dose (without doubling it). Patients should not discontinue Lopressor without consulting the physician.

Patients should be advised (1) to avoid operating automobiles and machinery or engaging in other tasks requiring alertness until the patient's response to therapy with Lopressor has been determined; (2) to contact the physician if any difficulty in breathing occurs; (3) to inform the physician or dentist before any type of surgery that he or she is taking Lopressor.

Laboratory Tests
Clinical laboratory findings may include elevated levels of serum transaminase, alkaline phosphatase, and lactate dehydrogenase.

Drug Interactions
Catecholamine-depleting drugs (e.g., reserpine) may have an additive effect when given with beta-blocking agents. Patients treated with Lopressor plus a catecholamine depletor should therefore be closely observed for evidence of hypotension or marked bradycardia, which may produce vertigo, syncope, or postural hypotension.

Risk of Anaphylactic Reaction. While taking beta-blockers, patients with a history of severe anaphylactic reaction to a variety of allergens may be more reactive to repeated challenge, either accidental, diagnostic, or therapeutic. Such patients may be unresponsive to the usual doses of epinephrine used to treat allergic reaction.

Carcinogenesis, Mutagenesis, Impairment of Fertility
Long-term studies in animals have been conducted to evaluate carcinogenic potential. In a 2-year study in rats at three oral dosage levels of up to 800 mg/kg per day, there was no increase in the development of spontaneously occurring benign or malignant neoplasms of any type. The only histologic changes that appeared to be drug related were an increased incidence of generally mild focal accumulation of foamy macrophages in pulmonary alveoli and a slight increase in biliary hyperplasia. In a 21-month study in Swiss albino mice at three oral dosage levels of up to 750 mg/kg per day, benign lung tumors (small adenomas) occurred more frequently in female mice receiving the highest dose than in untreated control animals. There was no increase in malignant or total (benign plus malignant) lung tumors, nor in the overall incidence of tumors or malignant tumors. This 21-month study was repeated in CD-1 mice, and no statistically or biologically significant differences were observed between treated and control mice of either sex for any type of tumor.

All mutagenicity tests performed (a dominant lethal study in mice, chromosome studies in somatic cells, a Salmonella/mammalian-microsome mutagenicity test, and a nucleus anomaly test in somatic interphase nuclei) were negative.

No evidence of impaired fertility due to Lopressor was observed in a study performed in rats at doses up to 55.5 times the maximum daily human dose of 450 mg.

Pregnancy Category C
Lopressor has been shown to increase postimplantation loss and decrease neonatal survival in rats at doses up to 55.5 times the maximum daily human dose of 450 mg. Distribution studies in mice confirm exposure of the fetus when Lopressor is administered to the pregnant animal. These studies have revealed no evidence of impaired fertility or teratogenicity. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers
Lopressor is excreted in breast milk in very small quantity. An infant consuming 1 liter of breast milk daily would receive a dose of less than 1 mg of the drug. Caution should be exercised when Lopressor is administered to a nursing woman.

Pediatric Use
Safety and effectiveness in children have not been established.

ADVERSE REACTIONS
Hypertension and Angina
Most adverse effects have been mild and transient.

Central Nervous System: Tiredness and dizziness have occurred in about 10 of 100 patients. Depression has been reported in about 5 of 100 patients. Mental confusion and short-term memory loss have been reported. Headache, nightmares, and insomnia have also been reported.

Cardiovascular: Shortness of breath and bradycardia have occurred in approximately 3 of 100 patients. Cold extremities; arterial insufficiency, usually of the Raynaud type; palpitations; congestive heart failure; peripheral edema; and hypotension have been reported in about 1 of 100 patients. (See **CONTRAINDICATIONS, WARNINGS,** and **PRECAUTIONS**.)

Respiratory: Wheezing (bronchospasm) and dyspnea have been reported in about 1 of 100 patients (see **WARNINGS**).

Gastrointestinal: Diarrhea has occurred in about 5 of 100 patients. Nausea, dry mouth, gastric pain, constipation, flatulence, and heartburn have been reported in about 1 of 100 patients.

Hypersensitive Reactions: Pruritus or rash have occurred in about 5 of 100 patients. Worsening of psoriasis has also been reported.

Miscellaneous: Peyronie's disease has been reported in fewer than 1 of 100,000 patients. Musculoskeletal pain, blurred vision, and tinnitus have also been reported.

There have been rare reports of reversible alopecia, agranulocytosis, and dry eyes. Discontinuation of the drug should be considered if any such reaction is not otherwise explicable.

The oculomucocutaneous syndrome associated with the beta blocker practolol has not been reported with Lopressor.

Myocardial Infarction
Central Nervous System: Tiredness has been reported in about 1 of 100 patients. Vertigo, sleep disturbances, hallucinations, headache, dizziness, visual disturbances, confusion, and reduced libido have also been reported, but a drug relationship is not clear.

Cardiovascular: In the randomized comparison of Lopressor and placebo described in the **CLINICAL PHARMACOLOGY** section, the following adverse reactions were reported:

	Lopressor	*Placebo*
Hypotension (systolic BP < 90 mmHg)	27.4%	23.2%
Bradycardia (heart rate < 40 beats/min)	15.9%	6.7%
Second- or third-degree heart block	4.7%	4.7%
First-degree heart block (P-R ≥ 0.26 sec)	5.3%	1.9%
Heart failure	27.5%	29.6%

Respiratory: Dyspnea of pulmonary origin has been reported in fewer than 1 of 100 patients.

Gastrointestinal: Nausea and abdominal pain have been reported in fewer than 1 of 100 patients.

Dermatologic: Rash and worsened psoriasis have been reported, but a drug relationship is not clear.

Miscellaneous: Unstable diabetes and claudication have been reported, but a drug relationship is not clear.

Potential Adverse Reactions
A variety of adverse reactions not listed above have been reported with other beta-adrenergic blocking agents and should be considered potential adverse reactions to Lopressor.

Central Nervous System: Reversible mental depression progressing to catatonia; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.

Cardiovascular: Intensification of AV block (see **CONTRAINDICATIONS**).

Hematologic: Agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

Hypersensitive Reactions: Fever combined with aching and sore throat, laryngospasm, and respiratory distress.

OVERDOSAGE
Acute Toxicity
Several cases of overdosage have been reported, some leading to death.

Oral LD_{50}'s (mg/kg): mice, 1158-2460; rats, 3090-4670.

Signs and Symptoms
Potential signs and symptoms associated with overdosage with Lopressor are bradycardia, hypotension, bronchospasm, and cardiac failure.

Treatment
There is no specific antidote.

In general, patients with acute or recent myocardial infarction may be more hemodynamically unstable than other patients and should be treated accordingly (see **WARNINGS, Myocardial Infarction**).

On the basis of the pharmacologic actions of Lopressor, the following general measures should be employed:

Elimination of the Drug: Gastric lavage should be performed.

Bradycardia: Atropine should be administered. If there is no response to vagal blockade, isoproterenol should be administered cautiously.

Hypotension: A vasopressor should be administered, e.g., levarterenol or dopamine.

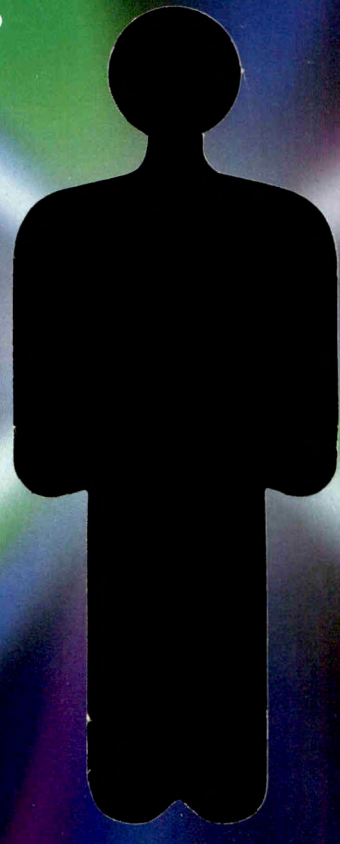
Bronchospasm: A beta$_2$-stimulating agent and/or a theophylline derivative should be administered.

Cardiac Failure: A digitalis glycoside and diuretic should be administered. In shock resulting from inadequate cardiac contractility, administration of dobutamine, isoproterenol, or glucagon may be considered.

Printed in U.S.A. C90-39 (Rev. 7/90)

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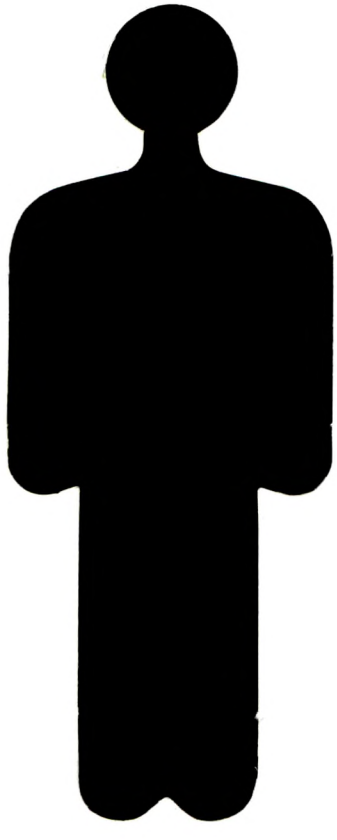
OMNIPAQUE®
(iohexol)
has a new image



Introducing

FLEXIPAK™ (Flexible Container)

A new package for OMNIPAQUE with safety, convenience and flexibility built in



The safety package

New FLEXIPAK makes it simple to purge air from the flexible container before hanging to help reduce the potential for air emboli. The easily spiked port eliminates the possibility of infusing microscopic rubber particles from glass-bottle stoppers. And you don't need an air vent because the soft sides collapse as OMNIPAQUE flows.

The convenience package

No more waste and messy cleanups from broken glass bottles. And, FLEXIPAK is ready and easy to hang, even on crowded IV poles. FLEXIPAK lightens the load from setup to administration and all points in between.

The flexibility package

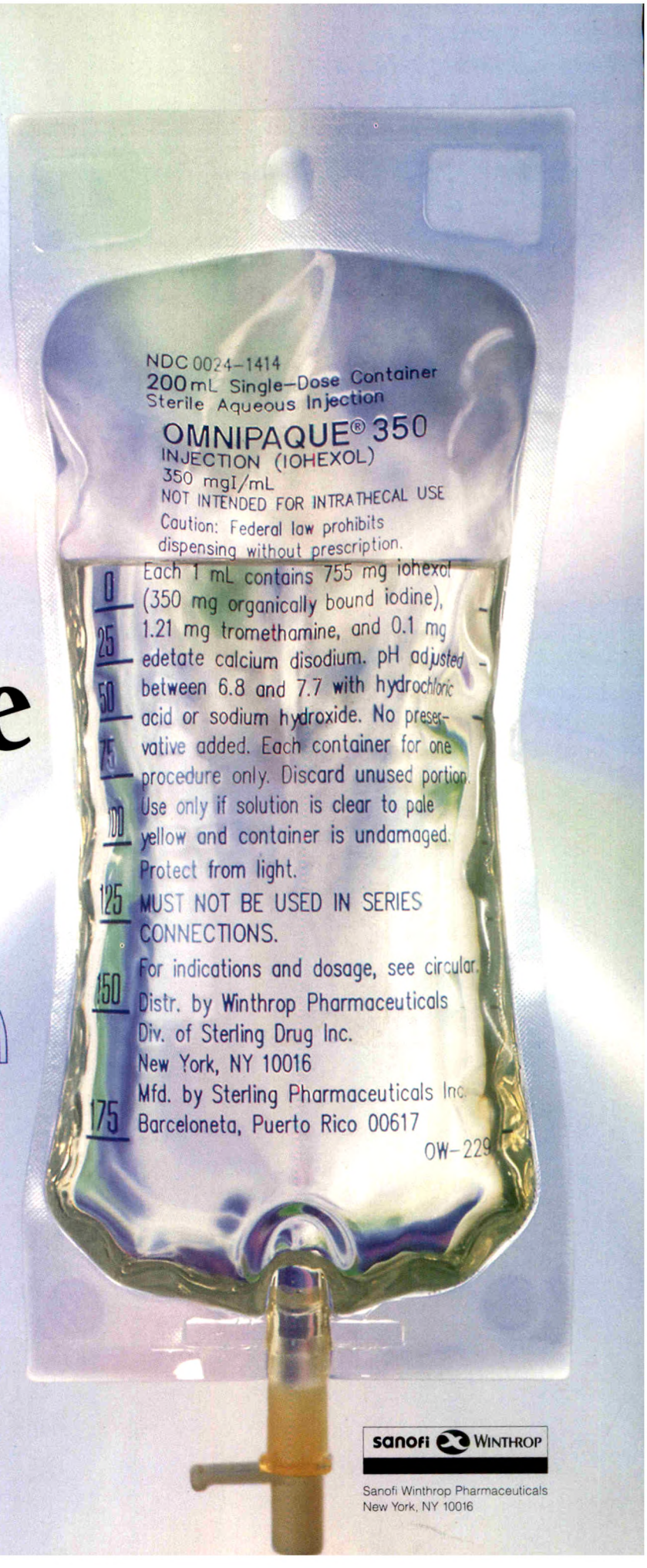
FLEXIPAK is flat and stackable for the best possible utilization of your storage space. And FLEXIPAK is available in the concentrations and sizes used most often.

	100 mL	150 mL	200 mL
OMNIPAQUE 240	x	x	x
OMNIPAQUE 300	x	x	
OMNIPAQUE 350	x	x	x

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It's all part of the package!

NONIONIC
OMNIPAQUE®
(IOHEXOL)



See last page for important product information concerning contraindications, warnings, adverse reactions, patient selection, and prescribing and precautionary recommendations.

All nonionic iodinated contrast media currently available inhibit blood coagulation, in vitro, less than ionic contrast media. Clotting has been reported when blood remains in contact with syringes containing nonionic contrast media. Therefore, meticulous intravascular administration technique is necessary to minimize thromboembolic events.

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Sanofi Winthrop Pharmaceuticals
New York, NY 10016

64-1121

OMNIPAQUE® 140 240 300 350
INJECTION (IOHEXOL)
INTRAVASCULAR

PLEASE CONSULT FULL PRODUCT INFORMATION BEFORE USING. A SUMMARY FOLLOWS:

DESCRIPTION: OMNIPAQUE is a sterile, pyrogen-free and preservative-free, nonionic, water-soluble radiographic contrast medium for intravascular administration in concentrations of 140, 240, 300, and 350 mgI/mL. OMNIPAQUE 140 contains 302 mg of iohexol equivalent to 140 mg of organic iodine per mL; OMNIPAQUE 240 contains 518 mg of iohexol equivalent to 240 mg of organic iodine per mL; OMNIPAQUE 300 contains 647 mg of iohexol equivalent to 300 mg of organic iodine per mL; and OMNIPAQUE 350 contains 755 mg of iohexol equivalent to 350 mg of organic iodine per mL. Each milliliter of iohexol solution contains 1.21 mg tromethamine and 0.1 mg edetate calcium disodium with the pH adjusted between 6.8 and 7.7 with hydrochloric acid or sodium hydroxide. Unused portions must be discarded. Iohexol solution is sensitive to light and should be protected from exposure.

CONTRAINDICATIONS: OMNIPAQUE should not be administered to patients with a known hypersensitivity to iohexol.

WARNINGS—General: Nonionic iodinated contrast media inhibit blood coagulation, in vitro, less than ionic contrast media. Clotting has been reported when blood remains in contact with syringes containing nonionic contrast media.

Serious, rarely fatal, thromboembolic events causing myocardial infarction and stroke have been reported during angiographic procedures with both ionic and nonionic contrast media. Therefore, meticulous intravascular administration technique is necessary, particularly during angiographic procedures, to minimize thromboembolic events. Numerous factors, including length of procedure, catheter and syringe material, underlying disease state, and concomitant medications, may contribute to the development of thromboembolic events. For these reasons, meticulous angiographic techniques are recommended including close attention to guidewire and catheter manipulation, use of manifold systems and/or three-way stopcocks, frequent catheter flushing with heparinized saline solutions and minimizing the length of the procedure. The use of plastic syringes in place of glass syringes has been reported to decrease but not eliminate the likelihood of in vitro clotting.

OMNIPAQUE should be used with extreme care in patients with severe functional disturbances of the liver and kidneys, severe thyrotoxicosis, or myelomatosis. Diabetics with a serum creatinine level above 3 mg/dL should not be examined unless the possible benefits of the examination clearly outweigh the additional risk. OMNIPAQUE is not recommended for use in patients with anuria.

Radiopaque contrast agents are potentially hazardous in patients with multiple myeloma or other paraproteinemia, particularly in those with therapeutically resistant anuria. Although neither the contrast agent nor dehydration has separately proven to be the cause of anuria in myeloma, it has been speculated that the combination of both may be causative factors. The risk in myelomatous patients is not a contraindication; however, special precautions are necessary. Partial dehydration in the preparation of these patients prior to injection is not recommended since this may predispose the patient to precipitation of the myeloma protein in the renal tubules. No form of therapy, including dialysis, has been successful in reversing the effect. Myeloma, which occurs most commonly in persons over age 40, should be considered before instituting intravascular administration of contrast agents.

Ionic contrast media, when injected intravenously or intra-arterially, may promote sickling in individuals who are homozygous for sickle cell disease.

Administration of radiopaque materials to patients known or suspected of having pheochromocytoma should be performed with extreme caution. If, in the opinion of the physician, the possible benefits of such procedures outweigh the considered risks, the procedures may be performed; however, the amount of radiopaque medium injected should be kept to an absolute minimum. The patient's blood pressure should be assessed throughout the procedure and measures for the treatment of hypertensive crisis should be readily available.

Reports of thyroid storm following the use of iodinated, ionic radiopaque contrast media in patients with hyperthyroidism or with an autonomously functioning thyroid nodule suggest that this additional risk be evaluated in such patients before use of any contrast medium.

Urography should be performed with caution in patients with severely impaired renal function and patients with combined renal and hepatic disease.

PRECAUTIONS—General: Diagnostic procedures which involve the use of radiopaque diagnostic agents should be carried out under the direction of personnel with the prerequisite training and with a thorough knowledge of the particular procedure to be performed. Appropriate facilities should be available for coping with any complication of the procedure, as well as for emergency treatment of severe reactions to the contrast agent itself. After parenteral administration of a radiopaque agent, competent personnel and emergency facilities should be available for at least 30 to 60 minutes, since severe delayed reactions have occurred (see ADVERSE REACTIONS: Intravascular—General).

Preparatory dehydration is dangerous and may contribute to acute renal failure in patients with advanced vascular disease, in diabetic patients, and in susceptible nondiabetic patients (often elderly with preexisting renal disease), infants, and small children. Dehydration in these patients seems to be enhanced by the osmotic diuretic action of urographic agents. It is believed that overnight fluid restriction prior to excretory urography generally does not provide better visualization in normal patients. *Patients should be well hydrated prior to and following administration of any contrast medium, including iohexol.*

Acute renal failure has been reported in diabetic patients with diabetic nephropathy and in susceptible nondiabetic patients (often elderly with preexisting renal disease) following excretory urography. Therefore, careful consideration of the potential risks should be given before performing this radiographic procedure in these patients.

Immediately following surgery, excretory urography should be used with caution in renal transplant recipients.

The possibility of a reaction, including serious, life-threatening, fatal, anaphylactoid or cardiovascular reactions should always be considered (see ADVERSE REACTIONS: Intravascular—General). It is of utmost importance that a course of action be carefully planned in advance for immediate treatment of serious reactions, and that adequate and appropriate personnel be readily available in case of any reaction.

The possibility of an idiosyncratic reaction in susceptible patients should always be considered (see ADVERSE REACTIONS: Intravascular—General). The susceptible population includes, but is not limited to, patients with a history of a previous reaction to contrast media, patients with a known sensitivity to iodine per se, and patients with a known clinical hypersensitivity: bronchial asthma, hay fever, and food allergies.

The occurrence of severe idiosyncratic reactions has prompted the use of several pretesting methods. However, pretesting cannot be relied upon to predict severe reactions and may itself be hazardous for the patient. It is suggested that a thorough medical history with emphasis on allergy and hypersensitivity, prior to the injection of any contrast media, may be more accurate than pretesting in predicting potential adverse reactions.

A positive history of allergies or hypersensitivity does not arbitrarily contraindicate the use of a contrast agent where a diagnostic procedure is thought essential, but caution should be exercised (see ADVERSE REACTIONS: Intravascular—General). Premedication with antihistamines or corticosteroids to avoid or minimize possible allergic reactions in such patients should be considered and administered using separate syringes. Recent reports indicate that such pretreatment does not prevent serious, life-threatening reactions, but may reduce both their incidence and severity.

Even though the osmolality of OMNIPAQUE is low compared to diatrizoate- or iothalamate-based ionic agents of comparable iodine concentration, the potential transitory increase in the circulatory osmotic load in patients with congestive heart failure requires caution during injection. These patients should be observed for several hours following the procedure to detect delayed hemodynamic disturbances.

General anesthesia may be indicated in the performance of some procedures in selected adult patients; however, a higher incidence of adverse reactions has been reported in these patients and may be attributable to the inability of the patient to identify untoward symptoms, or to the hypotensive effect of anesthesia, which can reduce cardiac output and increase the duration of exposure to the contrast agent.

Angiography should be avoided whenever possible in patients with homocystinuria, because of the risk of inducing thrombosis and embolism.

In angiographic procedures, the possibility of dislodging plaques or damaging or perforating the vessel wall should be borne in mind during the catheter manipulations and contrast medium injection. Test injections to ensure proper catheter placement are recommended.

Selective coronary arteriography should be performed only in those patients in whom the expected benefits outweigh the potential risk. The inherent risks of angiocardiography in patients with chronic pulmonary emphysema must be weighed against the necessity for performing this procedure.

When OMNIPAQUE is to be injected using plastic disposable syringes, the contrast medium should be drawn into the syringe and used immediately.

If nondisposable equipment is used, scrupulous care should be taken to prevent residual contamination with traces of cleansing agents.

Parenteral products should be inspected visually for particulate matter and discoloration prior to administration. If particulate matter or discoloration is present, do not use.

Information for Patients: Patients receiving injectable radiopaque diagnostic agents should be instructed to:

1. Inform your physician if you are pregnant.
2. Inform your physician if you are diabetic or if you have multiple myeloma, pheochromocytoma, homozygous sickle cell disease, or known thyroid disorder (see WARNINGS—General).
3. Inform your physician if you are allergic to any drugs, food, or if you had any reactions to previous injections of dyes used for x-ray procedures (see PRECAUTIONS—General).
4. Inform your physician about any other medications you are currently taking, including nonprescription drugs, before you are administered this drug.

Drug/Laboratory Test Interaction: If iodine-containing isotopes are to be administered for the diagnosis of thyroid disease, the iodine-binding capacity of thyroid tissue may be reduced for up to 2 weeks after contrast medium administration. Thyroid function tests which do not depend on iodine estimation, eg, T_3 resin uptake or direct thyroxine assays, are not affected. Many radiopaque contrast agents are incompatible in vitro with some antihistamines and many other drugs; therefore, no other pharmaceuticals should be admixed with contrast agents.

Carcinogenesis, Mutagenesis, Impairment of Fertility: No long-term animal studies have been performed to evaluate carcinogenic potential, mutagenesis, or whether OMNIPAQUE can affect fertility in men or women.

Pregnancy Category B: Reproduction studies have been performed in rats and rabbits with up to 100 times the recommended human dose. No evidence of impaired fertility or harm to the fetus has been demonstrated due to OMNIPAQUE. There are, however, no studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers: It is not known to what extent iohexol is excreted in human milk. However, many injectable contrast agents are excreted unchanged in human milk. Although it has not been established that serious adverse reactions occur in nursing infants, caution should be exercised when intravascular contrast media are administered to nursing women. Bottle feedings may be substituted for breast feedings for 24 hours following administration of OMNIPAQUE.

Pediatric Use: Pediatric patients at higher risk of experiencing adverse events during contrast medium administration may include those having asthma, a sensitivity to medication and/or allergens, congestive heart failure, a serum creatinine > 1.5 mg/dL, or those less than 12 months of age.

ADVERSE REACTIONS

Intravascular—General: Adverse reactions following the use of OMNIPAQUE are usually mild to moderate in severity. However, serious, life-threatening, and fatal reactions, mostly of cardiovascular origin, have been associated with the administration of iodine-containing contrast media, including OMNIPAQUE. The injection of contrast media is frequently associated with the sensation of warmth and pain, especially in peripheral angiography; pain and warmth are less frequent and less severe with OMNIPAQUE than with many contrast media.

Cardiovascular System: Arrhythmias including PVCs and PACs (2%), angina/chest pain (1%), and hypotension (0.7%). Others including cardiac failure, asystole, bradycardia, tachycardia, and vasovagal reaction were reported with an individual incidence of 0.3% or less. In controlled clinical trials involving 1,485 patients, one fatality occurred. A cause and effect relationship between this death and iohexol has not been established.

Nervous System: Vertigo [including dizziness and lightheadedness] (0.5%), pain (3%), vision abnormalities [including blurred vision and photomas] (2%), headache (2%), and taste perversion (1%). Others including anxiety, blurred vision, fever, motor and speech dysfunction, convulsion, paresthesia, somnolence, stiff neck, hemiparesis, syncope, shivering, transient ischemic attack, cerebral infarction, and nystagmus were reported, with an individual incidence of 0.3% or less.

Respiratory System: Dyspnea, rhinitis, coughing, and laryngitis, with an individual incidence of 0.2% or less.

Gastrointestinal System: Nausea (2%) and vomiting (0.7%). Others including diarrhea, dyspepsia, cramp, and dry mouth were reported, with an individual incidence of less than 0.1%.

Skin and Appendages: Urticaria (0.3%), purpura (0.1%), abscess (0.1%), and pruritus (0.1%).

Individual adverse reactions which occurred to a significantly greater extent for a specific procedure are listed under that indication in full prescribing information.

Pediatrics: In controlled clinical trials involving 391 patients for pediatric angiocardiography, urography, and contrast-enhanced computed tomographic head imaging, adverse reactions following the use of OMNIPAQUE 240, OMNIPAQUE 300 and OMNIPAQUE 350 were generally less frequent than with adults.

Cardiovascular System: Ventricular tachycardia (0.5%), 2:1 heart block (0.5%), hypertension (0.3%), and anemia (0.3%).
Nervous System: Pain (0.8%), fever (0.5%), taste abnormality (0.5%), and convulsion (0.3%).
Respiratory System: Congestion (0.3%) and apnea (0.3%).
Gastrointestinal System: Nausea (1%), hypoglycemia (0.3%), and vomiting (2%).
Skin and Appendages: Rash (0.3%).

General Adverse Reactions to Contrast Media: Physicians should remain alert for the occurrence of adverse effects in addition to those discussed above. The following reactions have been reported after administration of other intravascular iodinated contrast media, and rarely with iohexol. *Reactions due to technique:* hematomas and ecchymoses. *Hemodynamic reactions:* vein cramp and thrombophlebitis following intravenous injection. *Cardiovascular reactions:* rare cases of cardiac arrhythmias, reflex tachycardia, chest pain, cyanosis, hypertension, hypotension, peripheral vasodilatation, shock, and cardiac arrest. *Renal reactions:* occasionally, transient proteinuria; and rarely, oliguria or anuria. *Allergic reactions:* asthmatic attacks, nasal and conjunctival symptoms, dermal reactions such as urticaria with or without pruritus, as well as pleomorphic rashes, sneezing, and lacrimation; and rarely, anaphylactic reactions. Rare fatalities have occurred due to this or unknown causes. *Signs and symptoms related to the respiratory system:* pulmonary or laryngeal edema, bronchospasm, dyspnea; or *to the nervous system:* restlessness, tremors, convulsions. *Other reactions:* flushing, pain, warmth, metallic taste, nausea, vomiting, anxiety, headache, confusion, pallor, weakness, sweating, localized areas of edema (especially facial cramps), neutropenia, and dizziness. Rarely, immediate or delayed rigors can occur, sometimes accompanied by hyperpyrexia. Infrequently, "iodism" (salivary gland swelling) from organic iodinated compounds appears 2 days after exposure and subsides by the sixth day.

In general, the reactions which are known to occur upon parenteral administration of iodinated contrast agents are possible with any nonionic agent. Approximately 95% of adverse reactions accompanying the use of water-soluble intravascularly administered contrast agents are mild to moderate in degree. However, severe, life-threatening anaphylactoid reactions, mostly of cardiovascular origin, have occurred. Reported incidences of death range from 6.6 per 1 million (0.00066%) to 1 in 10,000 (0.01%). Most deaths occur during injection or 5 to 10 minutes later, the main feature being cardiac arrest, with cardiovascular disease as the main aggravating factor. Isolated reports of hypotensive collapse and shock are found in the literature. The incidence of shock is estimated to be 1 out of 20,000 (0.005%) patients.

Adverse reactions to injectable contrast media fall into two categories: chemotoxic reactions and idiosyncratic reactions.

Chemotoxic reactions result from the physicochemical properties of the contrast media, the dose, and the speed of injection. All hemodynamic disturbances and injuries to organs or vessels perfused by the contrast medium are included in this category.

Idiosyncratic reactions include all other reactions. They occur more frequently in patients 20 to 40 years old. Idiosyncratic reactions may or may not be dependent on the amount of dose injected, the speed of injection, and the radiographic procedure. Idiosyncratic reactions are subdivided into minor, intermediate, and severe. The minor reactions are self-limited and of short duration; the severe reactions are life-threatening and treatment is urgent and mandatory.

The reported incidence of adverse reactions to contrast media in patients with a history of allergy is twice that in the general population. Patients with a history of previous reactions to a contrast medium are three times more susceptible than other patients. However, sensitivity to contrast media does not appear to increase with repeated examinations.

Most adverse reactions to injectable contrast media appear within 1 to 3 minutes after the start of injection, but delayed reactions may occur.

Regardless of the contrast agent employed, the overall estimated incidence of serious adverse reactions is higher with angiocardiography than with other procedures. Cardiac decompensation, serious arrhythmias, angina pectoris, or myocardial ischemia or infarction may occur during angiocardiography and left ventriculography. Electrocardiographic and hemodynamic abnormalities occur less frequently with OMNIPAQUE than with diatrizoate meglumine and diatrizoate sodium injection.

CONSULT PACKAGE INSERT FOR A MORE DETAILED DISCUSSION OF ADVERSE REACTIONS FOR INTRAVASCULAR USE OF OMNIPAQUE.

OVERDOSAGE: Overdosage may occur. The adverse effects of overdosage are life-threatening and affect mainly the pulmonary and cardiovascular systems. The symptoms include cyanosis, bradycardia, acidosis, pulmonary hemorrhage, convulsions, coma, and cardiac arrest. Treatment of an overdosage is directed toward the support of all vital functions and prompt institution of symptomatic therapy.

The intravenous LD_{50} values of OMNIPAQUE (in grams of iodine per kilogram body weight) are 24.2 in mice and 15.0 in rats.

DOSAGE AND ADMINISTRATION: Details are provided in the package insert.

THE RADIOLOGICAL SOCIETY OF NORTH AMERICA

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64-1079

Outcome After Prolonged Balloon Inflations of >20 Minutes for Initially Unsuccessful Percutaneous Transluminal Coronary Angioplasty

John D. Jackman, Jr., MD, James P. Zidar, MD, James E. Tcheng, MD, Amy B. Overman, BSRT, Harry R. Phillips, MD, and Richard S. Stack, MD

Prolonged balloon inflation with or without autoperfusion techniques is a common initial approach to major dissection or abrupt occlusion after percutaneous transluminal coronary angioplasty (PTCA). To assess such a strategy in the setting of unsuccessful angioplasty, 40 patients who underwent prolonged balloon inflations of >20 minutes between January and July of 1991 after initially unsuccessful angioplasty were studied. These patients (median age 59 years) underwent PTCA for progressive or unstable angina (16 [40%]), symptomatic or asymptomatic residual stenosis after myocardial infarction (10 [25%]), acute myocardial infarction (3 [8%]), stable angina (3 [8%]), reinfarction (2 [5%]), and other indications (6 [15%]). The significant stenoses were primarily in the proximal and midportions of the right coronary (53%), left anterior descending (30%) and left circumflex (17%) coronary arteries. Before prolonged balloon inflation, the longest single inflation was 11 ± 6 minutes and the total time of all inflations was 17 ± 8 minutes (mean ± standard deviation). Stenosis was reduced from 91 ± 9 to 68 ± 16% before prolonged inflation. After prolonged balloon inflation of 30 ± 9 minutes, the residual stenosis was 47 ± 21% (p = 0.0001 vs value before prolonged inflation). Furthermore, improvements in the appearance of filling defects or dissections, or both, occurred in 19 patients (48%). Procedural success was obtained in 32 of 40 patients (80%). Coronary bypass grafting was performed in 8 patients (20%): 4 after unsuccessful PTCA (3 emergently) and 4 electively after initially successful PTCA. Although 5 patients had creatine kinase-MB elevations >20 IU/liter after the procedure, only 1 sustained a Q-wave myocardial infarction. There were no deaths in the hospital. In summary, prolonged balloon inflations of >20 minutes are successful in 80% of patients in whom initial extensive PTCA attempts were not. Prolonged inflations may thus be desirable before consideration of bypass grafting or stenting.

(Am J Cardiol 1992;69:1417–1421)

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Percutaneous transluminal coronary angioplasty (PTCA) has evolved over the past 15 years into a procedure with high success rates despite the increasing complexity of coronary lesions currently being treated.[1–5] Patients with multivessel disease, depressed ventricular function, eccentric stenoses in angulated segments, total occlusions, long lesions and bypass graft stenoses are receiving catheter-based coronary intervention with increasing frequency. Although success rates are in excess of 90% for most lesions treated, emergency coronary bypass grafting may be required in 1 to 3% of patients undergoing PTCA.[1–5] Surgical intervention may become necessary for major dissections which compromise coronary flow, persistence of severe stenosis despite repeated dilatations or abrupt occlusion. Current techniques exist that allow prolonged inflations in coronary arteries while maintaining flow to the distal myocardial bed.[6] Although these catheters have been used to provide perfusion in patients with left ventricular dysfunction and extensive myocardium at risk in the distribution of the treated vessel, there are little data regarding their efficacy in the setting of failed angioplasty. In many such cases, extensive efforts with various balloon sizes, inflation pressures and durations have yielded unacceptable results. The angiographer is then left with the decision to attempt prolonged balloon inflation, proceed with other coronary intervention such as atherectomy or stent implantation, or refer for bypass grafting. We thus sought to explore the utility of prolonged inflations of >20 minutes in patients who had initially unsuccessful PTCA despite multiple or extended inflations, or both, during the same procedure.

METHODS

Patient population: All patients who underwent coronary angioplasty with a >20 minute balloon inflation in the interventional laboratory at Duke University Medical Center from January 1, 1991, through July 31, 1991, were identified through the Duke Interventional Cardiology Databank. All procedural encounters were reviewed. Patients who had primary prolonged inflations of >20 minutes were excluded. A cohort of 40 consecutive patients who had prolonged inflations of >20 minutes after initially unsuccessful PTCA was thus identified.

Procedural data: Angioplasty was performed using standard techniques.[5] All patients were premedicated with aspirin 325 mg/day and dipyridamole 75 mg 3 times a day. Procedures were performed using a femo-

TABLE I Characteristics of the 40 Patients Receiving Prolonged Balloon Inflations

Median age (interquartile range)	59 (52–71)
Gender (% men)	26 (65%)
Cardiac risk factors	
Systemic hypertension*	23 (58%)
Diabetes mellitus	12 (30%)
Hypercholesterolemia†	15 (38%)
Cigarette smoker	29 (73%)
Family history‡	17 (43%)
Indications for PTCA	
Progressive or unstable angina	16 (40%)
Residual stenosis after MI	10 (25%)
Acute myocardial infarction	3 (8%)
Stable angina	3 (8%)
Reinfarction	2 (5%)
Other indications	6 (15%)
ACC/AHA lesion type§	
Type A	3 (7%)
Type B1	10 (25%)
Type B2	23 (58%)
Type C	4 (10%)

*Blood pressure >140/90 mm Hg.
†Total cholesterol >200 mg/dl.
‡Premature coronary disease aged <60 years.
§American College of Cardiology/American Heart Association Task Force.[9,10]
MI = myocardial infarction; PTCA = percutaneous transluminal coronary angioplasty.

ral artery approach. Intravenous heparin was administered to maintain an activated clotting time of >300 seconds during the procedure. The perfusion balloon catheters used included 2.5 to 4.0 mm Stack® perfusion catheters and 2.5 to 4.0 mm ACS RX perfusion catheters (Advanced Cardiovascular Systems Inc., Santa Clara, California). Patients routinely received intravenous heparin for 24 hours after PTCA and continuation of daily aspirin.

Clinical data: Routine demographic and clinical data were prospectively collected for each patient and entered into a computerized medical information system that had been previously described.[7,8] These data included diagnostic category, indication for angioplasty, procedural outcome and in-hospital complications. Indications for angioplasty included stable, progressive or unstable angina, symptomatic or asymptomatic residual stenosis after myocardial infarction, acute myocardial infarction and reinfarction. Major complications included death, myocardial infarction, major dissection, significant angiographic filling defect, emergency or elective coronary bypass grafting, and subsequent ischemia requiring further coronary intervention in the hospital.

Angiographic data: Lesions were assessed using angiography with multiple orthogonal views. All cineangiograms were reviewed assessing lesion characteristics before intervention, after initial balloon angioplasty prior to the prolonged inflation, and after prolonged balloon inflation.

Cineangiograms for each lesion were visually assessed by consensus of 2 experienced angiographers for morphologic features similar to those reported by the American College of Cardiology/American Heart Association Task Force[9,10] and for percent diameter stenosis in the most severe view using a previously validated[11,12] ordinal scale (0, <25, 25, 50, 75, 95, 100%). Quantitative measurements of minimal luminal diameter, percent diameter stenosis, percent area stenosis and lesion length were obtained using an automated edge-detection digital angiographic system (ARTREK version 10 software, ADAC Laboratories, Milpitas, California). In 3 patients, quantitative measurements were technically inadequate and visual estimation alone was used.

Procedural success was defined as a residual diameter stenosis of ≤50% in the absence of major complication. All angioplasty balloon catheters used in the procedure were recorded. The longest balloon inflation cycle, the maximal balloon inflation pressure in atmospheres, and the total time of inflation were recorded. Major dissection was defined as dissection greater than the length of the balloon or compromising blood flow, whereas minor dissection represented those of lesser degree. Morphologic descriptors to further define dissection included longitudinal, transverse and spiral. Angiographic filling defects were graded as absent, vascular haziness or discrete thrombus (small or large).

Data analysis: Baseline characteristics for patients are described in terms of the median, 25th and 75th percentile for continuous variables, and by percentages for discretely valued variables. Procedural results are expressed as mean ± 1 SD. The significance of changes from before to after percent stenosis was assessed with the Wilcoxon signed-rank test. Spearman correlation was used to assess the relation between the results obtained with the prolonged balloon inflation and those obtained with the initial angioplasty.

RESULTS

Demographics: During the period from January 1, 1991, through July 31, 1991, a total of 903 patients underwent coronary intervention at Duke University Medical Center. Review of the maximal duration of balloon inflation detected all patients who received inflations of >20 minutes. After the exclusion of patients who had primary prolonged inflations, 40 were identified who had inflations of >20 minutes for initially unsuccessful PTCA. Patient characteristics are described in Table I. The median age of the cohort was 59 years (range 52 to 71). Underlying cardiac risk factors included diabetes mellitus in 12 (30%), hypertension in 23 (58%), hypercholesterolemia in 15 (38%) and tobacco abuse in 29 (73%). Indications for PTCA were progressive or unstable angina in 16 (40%), symptomatic or asymptomatic residual stenosis after myocardial infarction in 10 (25%), acute myocardial infarction in 3 (8%), stable angina in 3 (8%), reinfarction in 2 (5%), and other indications in 6 (16%). Lesions were located primarily in the proximal and midportions of the right coronary (53%), left anterior descending coronary (30%) and left circumflex coronary (17%) arteries. Lesions treated were American College of Cardiology/American Heart Association type A in 3 patients (7%), type B1 in 10 patients (25%), type B2 in 23 patients (58%) and type C in 4 patients (10%) (Figure 1).

Initial angioplasty results: Patients underwent an average of 3 ± 2 balloon inflations before the prolonged balloon inflation. The average longest single inflation was 11 ± 6 minutes and the average total time of all

TABLE II Procedural Data of 40 Patients Receiving Prolonged Balloon Inflations

Before prolonged inflation	
Initial lesion stenosis	91 ± 9%
Lesion length	7.6 ± 4.7 mm
Minimal luminal diameter	0.8 ± 0.5 mm
Maximal balloon diameter	3.3 ± 0.4 mm
Inflation pressure (max. balloon)	7 ± 2 atm
No. of inflations	3 ± 2
Longest single inflation	11 ± 6 minutes
Total inflation time	17 ± 8 minutes
Residual lesion stenosis	68 ± 16%
Prolonged balloon inflation	
Balloon diameter	3.3 ± 0.4 mm
Inflation pressure	6 ± 1 atm
Duration of prolonged inflation	30 ± 9 minutes
Added duration of inflation	20 minutes
Improvement in dissection	7 (17.5%)
Improvement in filling defects	15 (37.5%)
Final lesion stenosis	47 ± 21%
Minimal luminal diameter	2.0 ± 0.6 mm
Procedural success*	32 (80%)

* Residual stenosis ≤ 50% without Q-wave myocardial infarction, coronary bypass grafting or death.
max. = maximal.

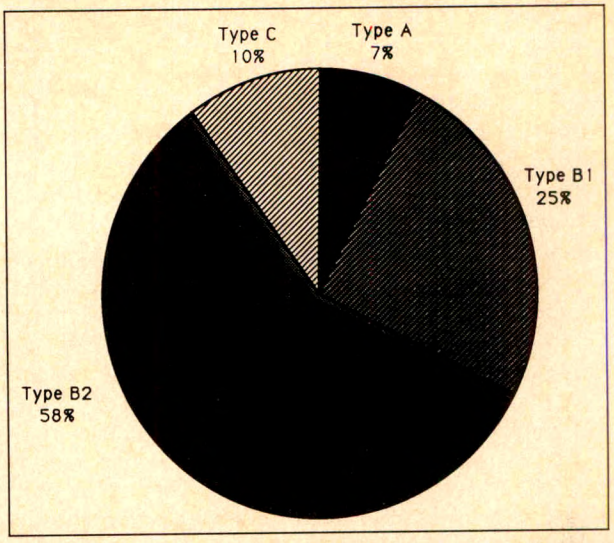


FIGURE 1. American College of Cardiology/American Heart Association lesion type of the 40 patients receiving prolonged balloon inflations.

inflations before prolonged inflation was 17 ± 8 minutes (mean ± SD). Before prolonged inflation, all patients had total inflation times >5 minutes, 80% >10 minutes, 65% >15 minutes, and 42% >20 minutes. Furthermore, 62% had a longest single inflation of >10 minutes and 40% had a longest single inflation of ≥15 minutes at some point before prolonged inflation.

The mean lesion length was 7.7 ± 4.8 mm by digital analysis. The mean stenosis was reduced from the initial 91 ± 9% to 68 ± 16% after these extensive angioplasty efforts. All patients thus had unsuccessful angioplasty results before prolonged balloon inflation. Major dissections occurred in 32 patients (80%), whereas minor dissections occurred in 3 (7.5%). Furthermore, 34 patients (85%) developed either haziness (n = 22) or discrete filling defects (n = 12) at the angioplasty site. One patient had neither dissection nor filling defect.

Prolonged balloon inflation results: The procedural results of initial angioplasty and prolonged balloon inflation are listed in Table II. Both the mean balloon diameter (3.3 ± 0.4 vs 3.3 ± 0.4 mm) and the mean inflation pressure (6 ± 1 vs 7 ± 1 atm) used for the prolonged inflation were similar to those immediately before the prolonged inflation. The average duration of prolonged balloon inflation was 30 ± 9 minutes (mean ± SD). After prolonged inflation, the degree of stenosis was reduced from 68 ± 16% to a residual 47 ± 21% (p = 0.0001 vs value before prolonged inflation) (Figure

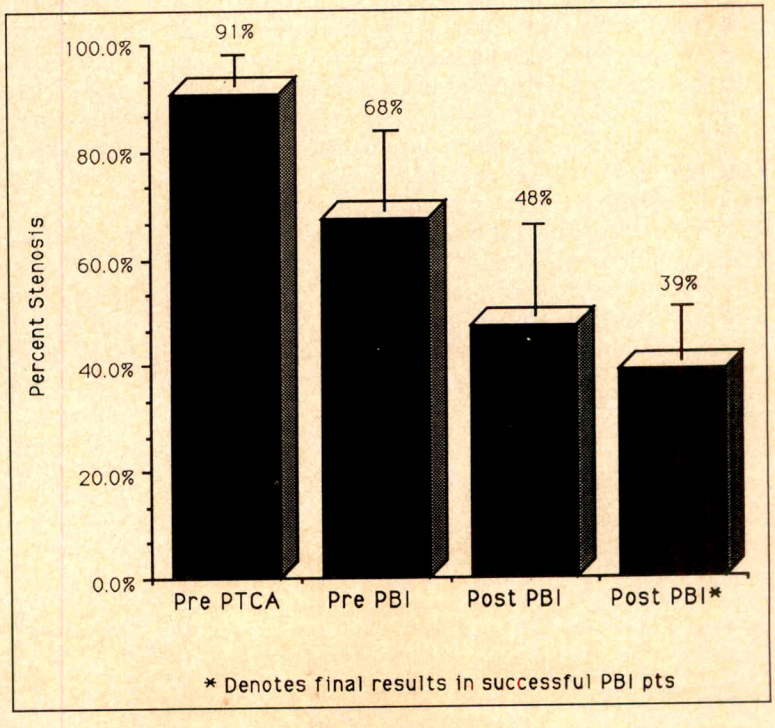


FIGURE 2. Percent diameter stenosis before initial percutaneous transluminal coronary angioplasty (PTCA), after initial angioplasty before prolonged balloon inflation (PBI), and after prolonged balloon inflation (total cohort and successful (*) prolonged inflation).

2). Spearman correlation between the initial angiographic result and the results of the prolonged inflation confirmed the contribution of the prolonged inflation while indicating further that this benefit is realized more strongly for patients experiencing minimal benefit from the initial inflations. Digital angiography confirmed that prolonged inflation yielded a reduction in the stenosis diameter from 77 ± 14% before intervention to a residual of 39 ± 18% ($p = 0.0001$). Area stenosis by digital angiography improved from 93 ± 7 to 58 ± 24% ($p = 0.001$), whereas the minimal luminal diameter increased from 0.8 ± 0.5 to 2.0 ± 0.6 mm ($p = 0.0001$). Additionally, improvement in the appearance of dissections occurred in 7 patients (17.5%) and improvement in the appearance of filling defects in 15 patients (37.5%). Overall, improvement in the appearance of filling defects or dissections, or both, occurred in 19 patients (48%). Blood flow graded according to the Thrombolysis in Myocardial Infarction trial improved after prolonged inflation from grade 2 to 3 in 2 patients, from grade 1 to 3 in 1 patient, and was unchanged in the remaining 37 (35 with grade 3, 1 with grade 2 and 1 with grade 0). Procedural success was obtained in 32 of the 40 patients (80%). The added duration of the prolonged inflation per patient (20 minutes) was similar in both successful and unsuccessful procedures.

Clinical outcome: Of the 8 patients with unsuccessful PTCA despite prolonged inflation, 3 (7.5%) underwent emergency coronary bypass grafting and a fourth later had elective coronary bypass grafting (Figure 3). In addition, 1 patient with unsuccessful prolonged inflation and suitable anatomy underwent salvage directional atherectomy with a successful outcome. One other patient with unsuccessful prolonged inflation had successful angioplasty the following day. The remaining 2 with unsuccessful prolonged inflations had no further intervention and no further ischemia or infarction in hospital. It should be noted that while other patients at this center underwent coronary stent placement, patients in this series with unsuccessful prolonged balloon inflation were not considered to have anatomy suitable for stenting.

Four patients with successful prolonged balloon inflations later underwent elective coronary bypass grafting in the hospital, 2 after recurrent angina and 2 after scheduled repeat catheterizations showed restenosis. The overall rate of coronary bypass grafting for all patients receiving prolonged inflations was thus 20% (8 patients). Another patient with successful prolonged balloon inflation developed angina and required repeat PTCA 3 days later. The overall rate of repeat PTCA in the hospital for patients receiving prolonged balloon inflations was 5% (2 patients).

Although 5 patients had creatine kinase-MB elevations of >20 IU/liter after the procedure, only 1 patient (2.5%) sustained a Q-wave myocardial infarction as a complication. No significant arrhythmic events occurred in hospital. There were no deaths in hospital.

DISCUSSION

Prolonged balloon inflations of >20 minutes confer an 80% success rate in patients who have received multiple and extended dilatations with initially unsuccessful coronary angioplasty results. Improvements in the appearance of dissections or filling defects occurred in 48% of patients. Furthermore, the rates of Q-wave myocardial infarction (2.5%), emergency bypass grafting (7.5%) and death (0%) were relatively low in this highly complex subset of patients who underwent initially unsuccessful angioplasty despite intensive efforts.

Autoperfusion during prolonged balloon inflations of up to 90 minutes has been associated with minimal reductions in regional coronary perfusion without significant myocardial ischemia or infarction in a number of experimental models.[13–18] Clinical studies have also demonstrated that perfusion balloon catheter inflations of 15-minute duration are well tolerated, with minimal or absent angina, electrocardiographic ischemia or myocardial necrosis.[19] Early clinical experience suggested that prolonged balloon inflations with a perfusion balloon catheter may result in successful revascularization and avoidance of surgery in patients who underwent initially unsuccessful PTCA.[6] Smith et al[20] reported that prolonged inflations resulted in successful outcomes in 16 of 28 patients (57%) after unsuccessful PTCA before 1989. Ten of the 12 patients with unsuccessful prolonged inflations required emergency coronary bypass grafting. More recently, Leitschuh et al[21] reported the outcome of prolonged inflations with perfusion balloon catheters in 36 patients with major dissection, and compared the results with those of historical control subjects with similar dissections before the availability of perfusion balloons. Angiographic success was 84% in the perfusion balloon group versus 62% in the conventional group. The complication rate was significantly lower in the perfusion balloon group, with 78% remaining free of major complication versus 48% in the conventional group. In this study, the mean total inflation time before perfusion balloon inflation was 7.8 minutes and the mean number of inflations was 6.5. However, no data

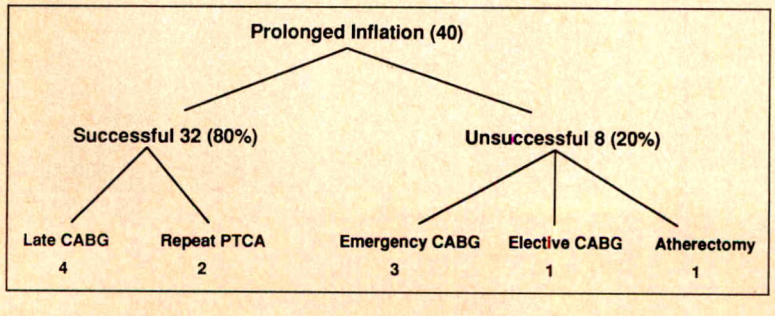


FIGURE 3. Clinical outcome of the 40 patients receiving prolonged balloon inflations. CABG = coronary artery bypass grafting; PTCA = percutaneous transluminal coronary angioplasty.

were provided regarding the degree of stenosis before the prolonged inflation, and thus the impact of the perfusion balloon inflation on the final result is uncertain. Furthermore, most patients received several short inflations without more extended inflations before the perfusion balloon inflation. Nonetheless, the success rate in their patients with major dissection was significantly improved compared with that of similar patients before the availability of perfusion balloon catheters.

We report the results of prolonged balloon inflation in patients with unsuccessful angioplasty despite both conventional and more extended inflations. The population reported in this study represents patients who remain refractory to aggressive angioplasty efforts, evidenced by the fact that prior to prolonged inflation 80% had total inflation times of >10 minutes and 65% of >15 minutes. Furthermore, 62% had a longest single inflation of >10 minutes, and 40% had a longest single inflation of ≥15 minutes. In addition, 50% of the patients had already received inflations with a perfusion balloon catheter. Despite these aggressive efforts, the patients had initially unsuccessful PTCA. Since neither the balloon diameter nor the inflation pressure differed significantly from that of the dilatations immediately before the prolonged inflation, the duration of the prolonged inflation appeared directly responsible for the successful outcomes obtained.

The primary question addressed was whether there was any benefit conferred by more prolonged balloon inflations of >20 minutes. If no benefit was achieved, earlier consideration of other strategies would be appropriate. Coronary atherectomy, stent implantation or earlier bypass grafting are some of the available options that could be pursued in a more timely manner if prolonged inflations of >20 minutes were found to be ineffective. However, we found that such prolonged inflations resulted in a significant improvement in the degree of stenosis and resulted in an 80% angiographic success rate. Furthermore, approximately half of the patients had improvement in the appearance of dissections or filling defects, or both.

The limitations of this study include its retrospective nature and the absence of a control group. The retrospective selection of patients with 20-minute inflations does not allow for a determination of the optimal inflation time for patients with initially unsuccessful angioplasty. A control group is not available because we empirically attempted prolonged balloon inflations before proceeding with coronary stenting or bypass grafting. Nevertheless, the results of our study provide further evidence that balloon angioplasty should not be considered unsuccessful until prolonged balloon inflation proves unsuccessful.

Acknowledgment: We wish to thank Gary L. Stiles, MD, for his thoughtful review of this manuscript, Charlotte M. Nelson, MS, for her assistance with statistical analysis, and Jessie Harrington and Carole Ross for their assistance in data collection.

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Referral Patterns and Exercise Response in the Rehabilitation of Female Coronary Patients Aged ≥62 Years

Philip A. Ades, MD, Mary L. Waldmann, BSN, Donna M. Polk, AB, and Janice T. Coflesky, PhD

Gender-related differences in cardiac rehabilitation referral patterns and response to an aerobic conditioning program were examined in 226 hospitalized older coronary patients (aged ≥62 years). Overall, the outpatient cardiac rehabilitation participation rate in this population was 21%. Older women were less likely to enter cardiac rehabilitation than were older men (15 vs 25%; p = 0.06), despite similar clinical profiles. This was explained primarily by a greater likelihood of primary physicians to strongly recommend cardiac rehabilitation to men. Before conditioning, women who entered cardiac rehabilitation were less fit than were men; peak oxygen consumption was 18% lower in women (16 ± 5 vs 20 ± 5 ml/kg/min; p = 0.02). However, both groups improved aerobic capacity similarly in response to a 12-week aerobic conditioning program, with maximal oxygen consumption increasing by 17% in women and by 19% in men. Thus, older female coronary patients are less likely to be referred for cardiac rehabilitation, despite a similar clinical profile and improvement in functional capacity from the training component.

(Am J Cardiol 1992;69:1422–1425)

Coronary heart disease is the leading cause of death in women, accounting for 50% of all deaths.[1] Coronary disease in women is primarily a disease of the later years, with the incidence increasing sharply after menopause.[2] Recent studies demonstrated both a higher in-hospital mortality rate and a greater likelihood of recurrent cardiac events in women after infarction than in men.[3] Despite these findings, women hospitalized for coronary heart disease undergo fewer major diagnostic and therapeutic procedures than do men.[4,5]

An important role for exercise-based cardiac rehabilitation has been demonstrated after myocardial infarction and coronary artery bypass surgery.[6–10] A systematic examination of participation patterns and training response in older female coronary patients has not been performed. Optimizing functional capacity in older female patients with advanced coronary heart disease may need closer supervision or different protocols than in male patients.[11–13]

The goals of this study were twofold: (1) to assess gender-related differences in cardiac rehabilitation participation in older postcoronary event patients, and (2) to examine differences in exercise capacity of older female and male patients before and after a 12-week supervised aerobic conditioning program.

METHODS

Subjects: Participation rates in the University of Vermont outpatient cardiac rehabilitation program were determined in 226 consecutive patients (43% women and 57% men, aged ≥62 years) who lived within 1 hour of the medical center and were hospitalized with acute myocardial infarction or coronary bypass surgery. The Medical Center Hospital of Vermont is a 500-bed tertiary care facility. This report limits itself to candidates from the local population of Burlington, Vermont (approximately 100,000). Patients referred from outlying hospitals were not considered in the referral aspect of this study. Data was collected from July 1988 through June 1991. Demographic, medical and social data were collected during an in-hospital guided interview to determine predictors of participation in older women and men. All patients interviewed were candidates for participation in cardiac rehabilitation ≥4 weeks after the cardiac event, after consulting with their physician. Shortly after the patient's initial outpatient visit with their physician, they were reinterviewed regarding cardiac rehabilitation participation and asked about the strength of their physician's recommendation for participation. This was scaled from 1 to 5 by the

From the Division of Cardiology, University of Vermont College of Medicine, Burlington, Vermont. Dr. Ades was supported by Clinical Investigator Award 1 K08 AG00426-01 from the National Institute on Aging, Bethesda, Maryland. Manuscript received December 13, 1991; revised manuscript received and accepted February 10, 1992.

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TABLE I Predictors of Cardiac Rehabilitation Participation

	Women	Men	p Value
Entry rate	15% (15/98)	25% (32/128)	0.06
Physician recommendation (scaled 1 to 5)	2.3 ± 2	3.0 ± 2	<0.05
Own and drive car	68% (67/98)	98% (125/128)	<0.001
Transportation problems	32% (31/98)	16% (20/128)	0.01
Marital status (% married)	44% (43/98)	79% (101/128)	<0.001
Arthritis	26% (25/98)	15% (19/128)	0.03
Dependent spouse	2.2 ± 1	1.6 ± 1	0.02

For scaled variables: 1 = minimal, and 5 = strong.

cardiac rehabilitation research nurse; 1 connoted that the physician did not recommend participation, 3 connoted perception of a moderate recommendation, and 4 and 5 represented a strong recommendation. Physicians were not directly questioned by study personnel, because direct questioning may alter physician behavior.

Symptom-limited treadmill testing was performed using a single MET (metabolic equivalent) increment modified Balke protocol[14] in the 57 patients who entered cardiac rehabilitation with collection of expired gas in a Hans-Rudolph mouthpiece. Subjects were studied while receiving their usual medications, with 45% of women, and 38% of men receiving β-adrenergic blocking drugs (p = not significant [NS]). Left ventricular ejection fraction was evaluated by cineangiography or radionuclide ventriculography. During exercise testing, expired gas was analyzed with a Sensormedics Horizon metabolic measurement cart (Sensormedics Corp., Yorba Linda, California), with oxygen consumption, carbon dioxide production, respiratory equivalent ratio and minute ventilation determined at 30-second intervals and at peak exercise. Exercise was terminated for general exhaustion or leg fatigue in all 57 patients. Only 2 patients described angina at peak exercise, and 3 had 1 to 2 mm of asymptomatic ST-segment depression on electrocardiogram.

Patients then entered a 12-week, 3 hour/week protocol of telemetry-monitored treadmill, and cycle and rowing ergometer exercise with intensity levels at 75 to 90% of maximal heart rate, as determined from their maximal stress test. Exercise was performed for 50 minutes/session, preceded by warm-up and stretching, and followed by cool-down. Subjects unable to sustain the full duration of exercise performed intermittent bouts to the full prescribed duration. After 36 sessions, subjects were retested on the treadmill.

Pre- and posttraining data within and between groups were analyzed by paired and independent sample *t* testing. Recruiting data were analyzed by the Wilcoxon rank sum test and chi-square analysis. Stepwise logistic regression analysis was performed to find a best-fitting model relating cardiac rehabilitation participation, and demographic and medical predictors of participation.

RESULTS

There was no difference between women and men in our hospitalized population in cardiac diagnosis (women: 53% infarction and 47% bypass surgery; and men: 43% infarction and 57% bypass surgery; p = NS), left ventricular ejection fraction (women 56 ± 13% and men 55 ± 13%; p = NS), duration of hospitalization (women: mean 22 ± 27 days and median 16; and men: mean 20 ± 21 days and median 15; p = NS), or incidence of noncardiac chronic disease (women 35 and men 37%; p = NS). Women were older than men (72 ± 7 vs 69 ± 5 years; p <0.05).

Older women were less likely than older men to enter the cardiac rehabilitation program (15 vs 25%; p = 0.06). Only 6% of women, and 7% of men did not complete the exercise program (p = NS). By stepwise logistic regression analysis, the strength of the physician recommendation was the most powerful predictor of participation for the entire group of 226 patients (mean recommendation score [scaled 1 to 5] 4.7 ± 8 in participants, and 1.9 ± 1.4 in nonparticipants [p <0.001]). However, physicians recommended participation more strongly to older men (mean score 3.0 ± 1.8) than to older women (mean score 2.3 ± 1.7; p <0.05), despite similar clinical profiles. Women had additional factors weighing against participation, because they were slightly older, less likely to own or drive a car, and more likely to have a dependent spouse at home and to have a diagnosis of arthritis (Table I). However, in the overall population, after factoring in the strength of the physicians' recommendation, none of the other factors noted above except age remained a significant predictor of participation by stepwise multivariate analysis. We performed a second stepwise multivariate analysis to determine the factors that predicted the physician recommendation score. Of the characteristics that differed between men and women (age, owning and driving a car, transportation problems, marital status, arthritis and dependent spouse), only age was a significant predictor of physician recommendation score (p = 0.025). Only 21% of the variance between women and men in the physician recommendation score was explained by differences in these characteristics in our best-fitting logistic regression model. Because Medicare, Medicaid and private medical insurance cover phase II cardiac rehabilitation services in Vermont, <5% of potential program candidates in this older age group were uninsured. Financial factors were not listed more often by women than by men as a constraint to participation, nor did genders differ in educational level or smoking status.

In the cardiac rehabilitation exercise program cohort (18 women and 39 men), there was no difference between women and men in age (women 70 ± 6 years [62

TABLE II Exercise Conditioning Data

	Women (n = 17)			Men (n = 37)		
	Preconditioning	Postconditioning	p Value	Preconditioning	Postconditioning	p Value
Maximal exercise						
$\dot{V}O_2$ (ml/kg/min)	16 ± 5	19 ± 5	<0.001	20 ± 5	23 ± 5	<0.001
Treadmill duration (min)	8 ± 4	13 ± 5	<0.001	9 ± 3	14 ± 5	0.001
RER (CO_2/O_2)	1.06 ± 14	1.02 ± .09	NS	1.05 ± .13	1.10 ± .15	NS
Ventilation (L/min)	44 ± 15	47 ± 15	NS	62 ± 18	60 ± 18	NS
HR (beats/min)	130 ± 20	131 ± 23	NS	128 ± 22	129 ± 18	NS
Systolic BP (mm Hg)	166 ± 22	169 ± 25	NS	161 ± 24	171 ± 25	<0.01
HR × BP	21,300 ± 6,270	22,300 ± 5,480	NS	19,500 ± 6,580	21,800 ± 6,570	0.07
Submaximal exercise (3 METS)						
Ventilation (L/min)	32 ± 7	27 ± 7	0.06	35 ± 6	29 ± 4	<0.001
HR (beats/min)	107 ± 21	95 ± 17	0.006	104 ± 18	90 ± 14	<0.001
Systolic BP (mm Hg)	144 ± 24	138 ± 23	0.03	143 ± 24	136 ± 25	NS
HR × BP	16,700 ± 4,200	13,600 ± 4,580	<0.01	14,800 ± 4,900	12,500 ± 3,490	<0.01
Resting						
HR (beats/min)	66 ± 13	67 ± 17	NS	72 ± 18	67 ± 8	0.01
Systolic BP (mm Hg)	126 ± 20	132 ± 16	NS	126 ± 18	130 ± 25	NS
HR × BP	8,200 ± 1,700	8,300 ± 3,740	NS	9,300 ± 2,800	8,800 ± 2,170	NS

BP = blood pressure; HR = heart rate; NS = not significant; RER = respiratory equivalent ratio (carbon dioxide production); $\dot{V}O_2$ = oxygen consumption.

to 82] and men 68 ± 5 years [62 to 80]), diagnosis (women 59% infarction and men 37% infarction), left ventricular ejection fraction (women 55 ± 12% and men 49 ± 14%) or frequency of β-blocker use (women 45% and men 38%; all p = NS). Two men and 1 woman withdrew from the exercise program. At baseline, women were less fit than were men (Table II). Maximal oxygen consumption was 18% lower (16 ± 5 vs 20 ± 5 ml/kg/min; p = 0.02), and duration of treadmill exercise was 16% shorter (8 ± 4 vs 9 ± 3 minutes; p = 0.07) in women. Older women were as likely as older men to attain a true maximal effort, as reflect by a peak respiratory equivalent ratio ≥1.00 (10 of 17 women vs 23 of 37 men; p = NS) or ≥1.10 (8 of 17 women vs 13 of 37 men; p = NS). Men attained a higher peak minute ventilation than did women. However, when normalized by body surface area (1.94 ± 0.14 m^2 in men vs 1.64 ± 0.16 m^2 in women), this difference was not significant.

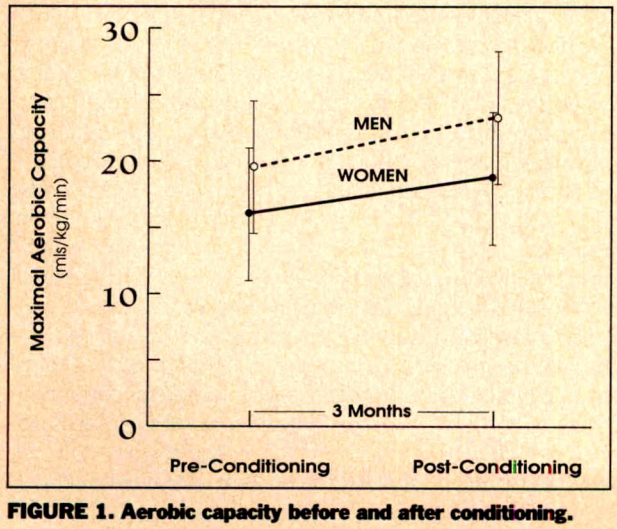


FIGURE 1. Aerobic capacity before and after conditioning.

With conditioning, women improved peak aerobic capacity significantly, with maximal oxygen consumption increasing by 17% (16 ± 5 to 19 ± 5 ml/kg/min). This was similar to the 19% increase noted in men (20 ± 5 to 23 ± 5 ml/kg/min; both p <0.001; Figure 1). Older women increased duration of treadmill exercise (8 ± 4 to 13 ± 5 minutes; p <0.001) to a similar degree as that of men. Body weight, rest and peak exercise heart rate and systolic blood pressure, and peak minute ventilation and respiratory equivalent ratio were unaffected by the conditioning process in older women (Table II).

After conditioning, older women manifested a more efficient response to submaximal exercise on the treadmill. At an exercise intensity of 3 METS, systolic blood pressure (144 ± 24 to 138 ± 23 mm Hg; p = 0.03), heart rate (107 ± 21 to 95 ± 17 beats/min; p = 0.006) and submaximal ventilation (32 ± 7 to 27 ± 7 liters/min; p = 0.06) decreased. These adaptations to the exercise program were similar to those seen in older men (Table II).

DISCUSSION

Cardiac rehabilitation has been proven to increase exercise capacity and decrease symptoms of ischemic heart disease in coronary patients.[6,15,16] In studies primarily of younger males after myocardial infarction, a diminished cardiac and overall mortality rate is suggested by meta-analysis of randomized trials.[9]

It was previously determined that older coronary patients are less likely to be referred for outpatient cardiac rehabilitation than are younger ones.[17] In this study, it was determined that older female coronary patients are less likely to participate in cardiac rehabilitation than are older men, despite clinical data that severity of disease was similar. The lower participation rate in older women was primarily due to a lower physician recom-

mendation score than that in men. Physician recommendation is the most powerful predictor of cardiac rehabilitation participation in older coronary patients.[18] Whether the lower physician recommendation is due to an impression that cardiac rehabilitation is less efficacious in women, a subtle manifestation of patient preference (i.e., women not wanting to exercise), or a straightforward bias could not be determined from our data. There remains the disturbing concern that as with cardiac catheterization in younger women with coronary heart disease,[4,5] physicians may pursue a less aggressive management approach in older women than in older men, despite a lower functional capacity that would normally warrant intensive rehabilitative efforts.

Most information about rehabilitation of female coronary patients has been extrapolated from data obtained in men. Our exercise data confirms that cardiac rehabilitation is as effective in older women as in older men in terms of increasing maximal exercise capacity. Although women were less fit than were men on entry in the program, they obtained the same relative training response to conditioning. The relative improvement in maximal oxygen consumption after conditioning was similar to that seen in studies of healthy older subjects.[19,20]

The lower aerobic capacity found in women at baseline may have been due to the relatively greater adiposity and lower fat-free body mass found in age-matched older women.[21] Normalized by estimates of fat-free body weight, oxygen consumption per kg of fat-free body weight/min was similar in men and women. This suggests that as with younger subjects, gender differences in aerobic capacity may be due to differences in body composition, rather than to inherent differences in cardiac or peripheral muscular function.[22]

Because coronary disease is increasingly becoming a disease of the later years, it is important for physicians to consider an intervention (such as cardiac rehabilitation) aimed at minimizing cardiac disability. Increased participation rates may be attained in older coronary patients if physicians acknowledge that their recommendation is a primary determinant of cardiac rehabilitation participation and that benefits of exercise in older women are similar in magnitude to those in men. Patients should be counseled both in the hospital and after discharge concerning the role of regular exercise in minimizing cardiac disability. Rehabilitation programs should consider the importance of establishing specific exercise programs for older patients and women, because patients may have misconceptions concerning the intensity of exercise to be performed.

Acknowledgment: We thank Eric T. Poehlman, PhD, for reviewing the manuscript, and Mary Grunwald, RPT, Sharon Beebe, RPT, and Kimberly Adams, BA, for coordinating training and testing.

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REVIEW

Amount of Exercise Necessary for the Patient with Coronary Artery Disease

Barry A. Franklin, PhD, Seymour Gordon, MD, and Gerald C. Timmis, MD

Exercise training can both protect against and provoke sudden coronary death.[1] Accordingly, we are obliged to provide "safe" exercise recommendations, reducing the risk of cardiovascular complications to a minimum, while prescribing sufficient exercise to promote desired training effects. The intensity of exercise needed to attain health-related benefits may differ from what is generally prescribed for cardiorespiratory conditioning. Lower levels of physical activity than previously recommended have been shown to reduce the risk of certain chronic degenerative diseases and yet be insufficient to improve the aerobic capacity or maximal oxygen uptake ($\dot{V}O_2$max).[2] Low to moderate intensity exercise training (≤60% $\dot{V}O_2$max) can elicit beneficial physiologic and psychosocial changes and possibly reduce cardiovascular-related mortality. Moreover, it appears that low- and high-intensity exercise training regimens produce comparable improvements in functional capacity and high-density lipoprotein (HDL) cholesterol, at least over the initial 3 months of conditioning.[3] This review clarifies the amount of exercise required to promote favorable adaptation and improvement in functional capacity, cardiac function, coronary risk factors, psychosocial well-being and morbidity/mortality (Figure 1) in patients with coronary artery disease (CAD).

Functional capacity: Recent studies suggest that low to moderate intensity exercise training will maintain or improve, or both, functional capacity after an acute coronary event. Simple exposure to orthostatic or gravitational stress during the bed rest stage of hospital convalescence may obviate much of the deterioration in exercise performance that follows myocardial infarction.[4] Moreover, a "spontaneous" increase in $\dot{V}O_2$max occurs in many deconditioned patients with CAD soon after hospital discharge,[5] presumably because the aerobic requirements of many daily activities exceed the "threshold" intensity for training.[6]

EFFECTS OF BED REST ON AEROBIC CAPACITY AND BENEFIT OF REGULAR CARDIOVASCULAR ORTHOSTATIC STRESS: Prolonged bed rest is seldom used any more in the care of patients with CAD because of the shortened hospital stay. Nevertheless, it has been shown to result in physiologic deconditioning and a significant decrease in the $\dot{V}O_2$max.[7] Although a traditional explanation for this phenomenon is the absence of daily physical activity, it appears that the deterioration in performance may simply reflect the lack of exposure to chronic orthostatic stress.

Convertino et al[8] studied changes in $\dot{V}O_2$max before and after 14 days of bed rest using daily 210-minute treatments using a reverse gradient garment that simulated the effects of standing. The $\dot{V}O_2$max decreased only 6% in subjects who received venous pooling treatment, compared with a 15% decrease in nontreated subjects (Table I). Moreover, a significantly greater decrease in $\dot{V}O_2$max has been demonstrated during upright than during supine exercise after bed rest, i.e., 17 versus 7%.[9] These data have important implications for inpatient cardiac rehabilitation. The loss of exposure to gravitational stress alone during the bed rest phase of hospital convalescence contributes to the reduction in $\dot{V}O_2$max after myocardial infarction, independent of myocardial damage. Thus, it appears that the deterioration in exercise performance with bed rest may be lessened simply by regular exposure to orthostatic stress, such as intermittent sitting or standing during the hospital confinement period.[4] Structured, formalized in-hospital exercise programs after acute myocardial infarction appear to offer little additional physiologic or behavioral (self-efficacy) benefits over routine medical care.[10,11]

SPONTANEOUS IMPROVEMENT IN AEROBIC CAPACITY: A significant increase in aerobic capacity, corresponding to 2 to 3 METs (1 MET = 3.5 ml O_2/kg/min), generally occurs between 3 and 11 weeks after clinically uncomplicated myocardial infarction, even in patients who undergo no formal exercise training (Figure 2).[12] Similar improvements have been reported for patients who have undergone percutaneous transluminal coronary angioplasty[13] or coronary revascularization surgery.[14] This spontaneous improvement in aerobic capacity has, from a hemodynamic perspective, been attributed to increases in peak heart rate and oxygen pulse, the latter reflecting increases in stroke volume, arteriovenous oxygen difference, or both.[12] Research indicates that self-care and other out-of-hospital activities performed by cardiac patients soon after hospital discharge frequently lead to sustained increases in heart rate and oxygen uptake that exceed frequently recommended levels for home activities.[6] These transient fluxes in cardiorespiratory activity may promote a training effect and account, at least in part, for the spontaneous improvement in aerobic capacity during the early weeks after myocardial infarction.

DeBusk et al[5] studied 70 patients with CAD soon after hospital discharge to assess whether the spontaneous increase in $\dot{V}O_2$max could be further augmented

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with exercise training. After symptom-limited treadmill exercise testing 3 weeks after infarction, 40 men were assigned to undergo 8 weeks of home (n = 12) or medically supervised gymnasium (n = 28) exercise training, whereas the remaining 30 served as control subjects, receiving no formal exercise instructions. During this 8-week interval, peak oxygen uptake increased significantly in all 3 groups: gymnasium training, from 6.6 to 11.0 METs (66%); home training, from 7.3 to 10.3 METs,

TABLE I Mean Changes in Maximal Oxygen Uptake ($\dot{V}O_2$max) Before and After Bed Rest

Remedial Treatment Mode	Bed Rest (days)	$\dot{V}O_2$max (liters/min)		
		Before	After	% Δ
None	14	3.9	3.3	−15
Venous pooling	14	3.3	3.1	−6

Adapted from *J Appl Physiol.*[8]
% Δ = percent change.

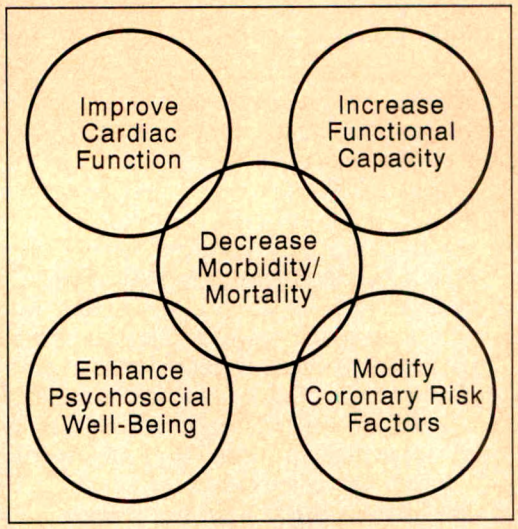


FIGURE 1. Common rationale for exercise training of patients with coronary artery disease.

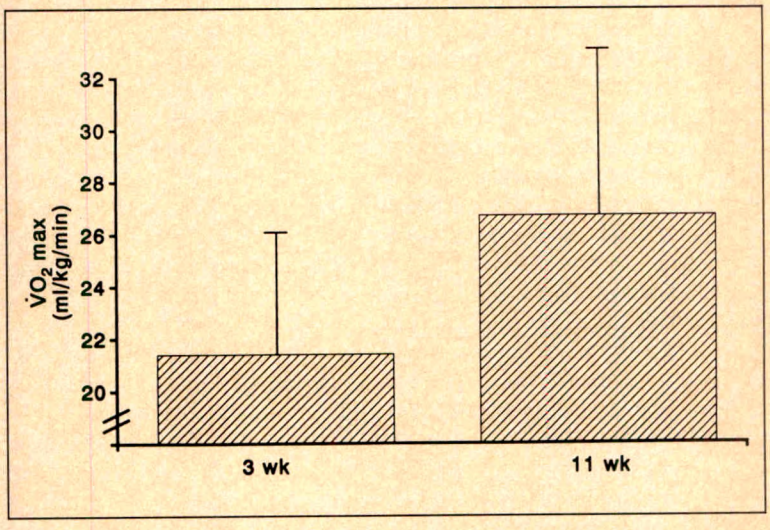


FIGURE 2. Improvement in aerobic capacity (maximal oxygen uptake [$\dot{V}O_2$ max]), expressed as ml/kg/min, after clinically uncomplicated myocardial infarction in patients who underwent no formal exercise training. Values represent mean ± SD ($p < 0.001$). (Adapted from Savin et al.[12])

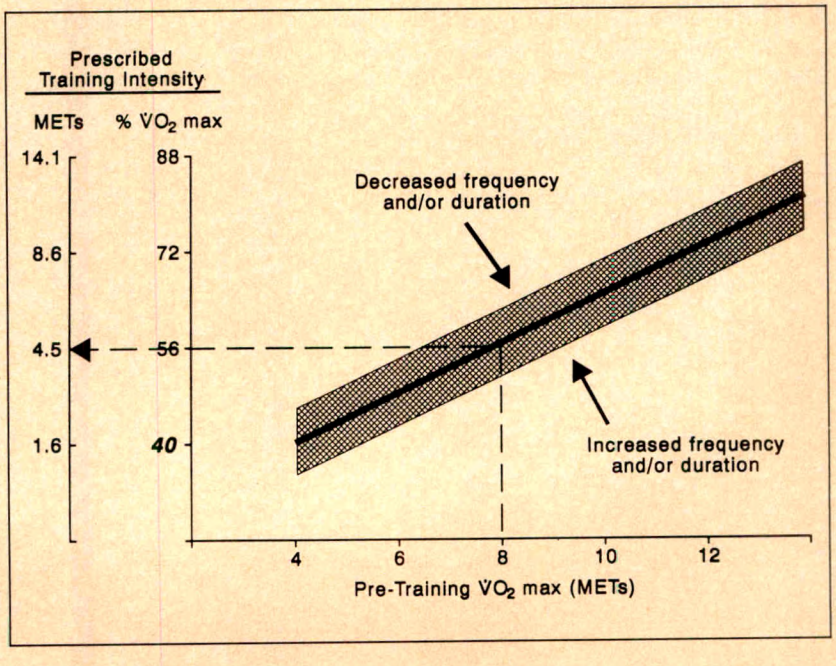


FIGURE 3. Theoretical relation between aerobic capacity (METs) and the minimal intensity for exercise training, expressed as a percentage of the maximal oxygen uptake ($\dot{V}O_2$ max). The threshold intensity for training increases in direct proportion to $\dot{V}O_2$ max before training; however, it can be modulated by altering the exercise duration or frequency, or both. For example, a patient with a peak capacity of 8 METs would exercise at approximately 56% of his $\dot{V}O_2$ max, or 4.5 ± 0.5 METs, to further increase his functional capacity.

(41%); and no training, from 7.0 to 9.4 METs (34%). The investigators concluded that formal exercise training soon after clinically uncomplicated myocardial infarction may not be required to restore aerobic capacity "to values approximating those of sedentary men of similar age without heart disease."

THRESHOLDS FOR TRAINING: For most deconditioned adults and patients with CAD, the threshold intensity for exercise training probably lies between 40 and 60% of the $\dot{V}O_2$max.[15] Improvement in aerobic capacity with low to moderate training intensities suggests that the interrelation among the training intensity, frequency and duration may permit a decrease in the intensity to be partially or totally compensated for by increases in the exercise duration or frequency, or both (Figure 3). Moreover, recent studies have shown similar training effects in subjects who completed three 10-minute bouts of moderate intensity exercise per day versus those who performed one "long" exercise bout of 30 minutes, 5 days per week for 8 weeks.[16] Thus, relative increases in functional capacity appear to depend more on the subject's initial fitness and the total amount of exercise accomplished or calories expended, than on the specific exercise frequency, intensity or duration.

TRAINING ACTIVITIES: VALUE OF WALKING: The most effective training activities employ large muscle groups, are maintained continuously, and are rhythmic and aerobic in nature; examples include walking and jogging, swimming, and mobile or stationary cycle ergometry. Walking is the most facile and easily regulated exercise for cardiorespiratory conditioning. Extremely slow walking (<2 miles per hour) approximates 2 METs and may impose metabolic loads sufficient for exercise training in deconditioned subjects.[17] Moreover, fast walking provides an intense enough activity to increase aerobic capacity and decrease body weight and fat stores in sedentary, middle-aged men.[18] In 1 study of 343 healthy adults (165 men, 178 women), 67% of men and 91% of women achieved a training heart rate (defined as ≥70% of maximal heart rate) when asked to "walk" a mile briskly.[19] In men >50 years of age, 83% achieved a training heart rate. These findings suggest that many patients with CAD can improve cardiorespiratory fitness by walking alone.

Cardiac function: The effects of chronic exercise training on the autonomic nervous system act to reduce myocardial demands at rest and during exercise. Vagal tone appears to be increased at rest, whereas sympathoadrenergic drive (circulating catecholamines, particularly norepinephrine) is decreased during exercise.[20] The result is a reduction in the heart rate–blood pressure product at any given oxygen uptake or submaximal work load, even when low to moderate exercise training intensities are used.[21]

The effects of physical conditioning on myocardial perfusion and ejection fraction are less clear. It has been suggested that a higher heart rate–blood pressure product at the onset of angina or ischemic ST-segment depression, or both, may reflect an improved myocardial oxygen supply. Some investigators have used thallium-201 exercise testing and multiple-gated image acquisition scans on subjects before and after training programs to assess changes in cardiac function. Although the findings have been contradictory, improvements have been reported both with and without vigorous exercise training regimens. In contrast, angiographic studies in group exercise trials have, without exception, yielded disappointing results.[22]

Ehsani et al[23] showed that prolonged and intense medically supervised endurance exercise training can, in selected cardiac patients, result in a higher heart rate–blood pressure product at the onset of ischemic ST-segment depression (≥0.1 mV), implying an increase in the delivery of oxygen to the myocardium. This regimen (80 to 90% of $\dot{V}O_2$max for 1 hour, 4 to 5 sessions per week for 1 year) also resulted in improvements in stroke volume and ejection fraction, suggesting a direct cardiac benefit in some, but not all patients.[24] More recently, Schuler et al[25] studied the effects of a low-fat/low-cholesterol diet and regular, high-intensity exercise in patients with CAD. After 1 year, patients demonstrated less exercise-induced myocardial ischemia by scintigraphic criteria, despite an increased peak heart rate–blood pressure product. Similar benefits, however, have

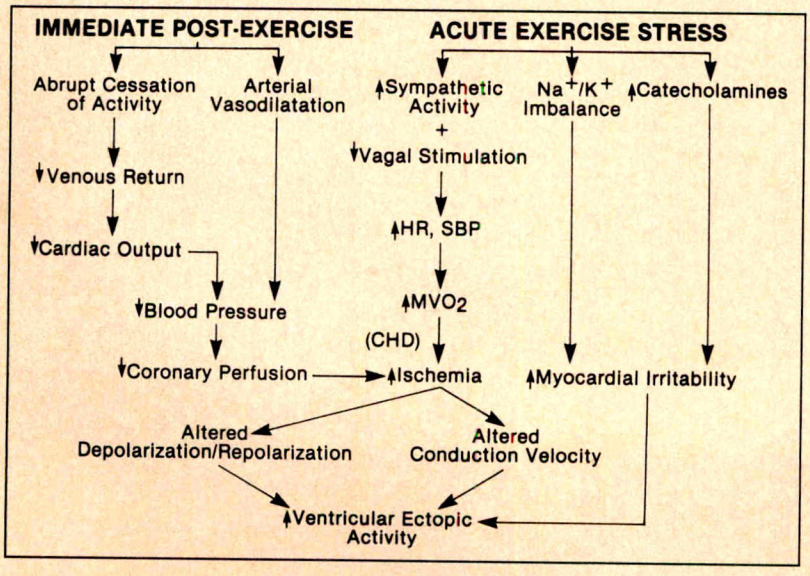


FIGURE 4. Physiologic alterations accompanying acute exercise and recovery, and their possible sequelae. CHD = coronary heart disease; HR = heart rate; MVO_2 = myocardial oxygen uptake; NA^+/K^+ = sodium/potassium ion; SBP = systolic blood pressure. (Reprinted with permission from *J Cardiac Rehabil.*[29])

been demonstrated with more moderate exercise training regimens. For example, Laslett et al[26] reported an increase in the heart rate–blood pressure product at the onset of ischemic ST-segment depression in exercise-trained patients with CAD. Froelicher et al[27] used thallium-201 exercise testing and multiple-gated image acquisition analysis scans on subjects before and after a combined arm-leg training program that lasted 3 to 12 months. Six of 16 patients showed improvement in left ventricular ejection fraction or exercise thallium images, or both, after training. Of the remaining 10 patients, 2 had images that worsened and 8 showed no change.

SAFETY OF HIGH-INTENSITY TRAINING REGIMENS: The incidence of cardiovascular complications during exercise is considerably greater among cardiac patients than among presumably healthy adults. Cobb and Weaver[28] emphasized that cardiac arrest associated with exercise testing and training in patients with CAD is typically a primary arrhythmic event not due to acute myocardial infarction. The additional risk of cardiac arrest during exercise, compared with that at other times, may be >100-fold during or soon after vigorous physical exertion.

By increasing myocardial oxygen demands and simultaneously shortening diastole, and thus coronary perfusion time, exercise may evoke a transient oxygen deficit in the subendocardial tissue, which can be exacerbated by a decreased venous return secondary to abrupt cessation of activity. Ischemia can alter repolarization, depolarization and conduction velocity, triggering serious ventricular arrhythmias which, in extreme cases, may be the harbingers of ventricular tachycardia or fibrillation, or both. Furthermore, intracellular sodium-potassium imbalance, catecholamine excess and increased sympathetic outflow may be arrhythmogenic (Figure 4).[29]

The safety of high-intensity exercise training regimens has been challenged in retrospective reports of patients with CAD who developed cardiac arrest or ventricular fibrillation during or shortly after medically supervised rehabilitation exercise.[30,31] Hossack and Hartwig[31] identified patients at increased risk of untoward events as those having a markedly ischemic exercise electrocardiogram, an above-average functional capacity, or a record of poor compliance to the prescribed training heart rate range (i.e., exercise intensity violators). These and other recent data[32] suggest that unconventionally vigorous exercise is associated with an increased risk of cardiovascular complications in patients with CAD.

Coronary risk factors: Aerobic exercise training programs can result in moderate losses in body weight, moderate to large losses in body fat, and small to moderate increases in lean body weight. Endurance exercise can also promote decreases in blood pressure (particularly among hypertensives),[33] total blood cholesterol, serum triglycerides, and low-density lipoprotein (LDL) cholesterol, and increases in the "antiatherogenic" HDL cholesterol subfraction.[34]

OBESITY: Exercise programs to reduce body weight and fat stores should be performed at least 3 days/week and include sustained activity of an endurance nature to promote a caloric expenditure of 300 to 500 kcal per session.[15] For many patients this may be best accomplished by regular walking over an extended duration. Exercise rated between "fairly light" and "somewhat hard" is generally appropriate for weight reduction programs, corresponding to 60 to 70% of the maximal heart rate, which is equivalent to 40 to 60% $\dot{V}O_2$max. During this relative intensity, free fatty acids are used preferentially as a fuel source, while blood lactate levels generally remain low, allowing the individual to exercise for sustained periods.

TABLE II Effects of Exercise on Total and Low-Density Lipoprotein Cholesterol with Body Weight Changes

Body Weight	Total Cholesterol (mg/dl)	LDL Cholesterol (mg/dl)
→	−7*	−3*
↓	−13*	−11*
↑	+3	+3

*$p < 0.05$.
Adapted from *JAMA*.[38]
LDL = low-density lipoprotein; → = no change; ↓ = decrease; ↑ = increase.

HYPERTENSION: A meta-analysis of 25 relevant studies over the last 20 years appears to strengthen the case for moderate-intensity exercise training in the treatment of mild hypertension.[35] The studies involved men between 15 and 70 years of age and the training programs varied from 1 to 12 months in duration. Approximately two-thirds of the experimental groups in these studies demonstrated statistically significant decreases in blood pressure, averaging about 10 mm Hg for both systolic and diastolic blood pressure. Moderate-intensity training, corresponding to 40 to 60% $\dot{V}O_2$max, seemed to be just as effective as high-intensity training, and possibly even more so. Recent studies suggest that moderate aerobic exercise should not be considered a replacement for pharmacologic therapy in patients with mild hypertension.[36]

BLOOD LIPIDS AND LIPOPROTEINS: The results of 66 exercise studies, statistically aggregated using meta-analysis, showed that physical training produced modest changes in blood lipids and lipoproteins.[37] In the average exercising subject, total cholesterol decreased 10 mg/dl ($p < 0.01$), total triglycerides decreased by 16 mg/dl ($p < 0.01$), HDL cholesterol increased by 1 mg/dl (p = not significant), LDL cholesterol decreased by 5 mg/dl ($p < 0.05$), and the total/HDL cholesterol ratio decreased by 0.5 ($p < 0.01$). None of the changes for the control groups were significant. Higher initial levels of total cholesterol, total triglyceride, and total/HDL cholesterol ratio, and lower initial levels of HDL cholesterol, resulted in greater postconditioning decreases and increases, respectively. Although total cholesterol decreased as the exercise duration (hours) increased, lower training intensities were associated with more beneficial changes in lipids and lipoproteins.

As a follow-up to this analyses, data from 95 exercise studies were partitioned into those in which subjects gained, maintained, or lost body weight.[38] When body weight decreased or remained unchanged, total cholesterol and LDL cholesterol levels decreased significantly

TABLE III Cardiac Rehabilitation Trial Results

Trials	No. of Pts. Randomized		Entry after MI (mos)	Length of Follow-Up (mos)	Deaths (no.)		Mortality (%)		Effectiveness (%)
	Control	Intervention			Control	Intervention	Control	Intervention	
Sanne[47]	157	158	3	48	35	28	23	18	22
Hakkila[48]	81	77	On hospital discharge	24	10	8	12	10	15
Kentala[49]	146	152	2	12	32	26	22	17	22
Palatsi[50]	200	180	2	29	28	18	14	10	29
Kallio[51]	187	188	1	36	56	41	30	22	27
Shaw[52]	328	323	2–12	30–54	24	15	7	5	37
Shephard[53]	354	379	12	48	26	36	7	10	−30
Roman[54]	100	93	2	108	27	16	6	4*	38

*Mortality expressed in %/year of patients followed up.
MI = myocardial infarction.

(Table II). However, when body weight increased, cholesterol and LDL cholesterol levels increased. These results suggest that exercise-mediated reductions in cholesterol and LDL cholesterol are greatest when concomitant body weight losses occur.

Although cross-sectional and longitudinal comparisons have shown that vigorous physical activity is associated with an increased HDL cholesterol, recent studies indicate that chronic low-intensity, long duration physical activity (measured in miles walked per day) may play an important role in increasing both the HDL cholesterol and HDL_2 cholesterol.[39] It has been suggested that approximately 1,000 kcal per week of additional energy expenditure, equivalent to walking or running 8 to 10 miles, may represent the threshold required to increase HDL cholesterol.[40] However, prospective studies in cardiac patients have shown that increases in HDL cholesterol may be achieved at an even lower exercise dosage.[34,41]

Psychosocial well-being: Another rationale for exercise training of patients with CAD is that it improves psychosocial functioning. Anecdotal reports and uncontrolled studies frequently describe improvements in psychological well-being in relation to exercise-based cardiac rehabilitation programs. Subjective comments of improvement after exercise training often include an increase in self-confidence, particularly in relation to exertional tasks, an improved sense of well-being, decreased depression and hypochondriasis levels, reduced tension and fatigue, better sleep, and improved sexual relations. However, it remains unclear to what extent these changes reflect the exercise program, per se, or "spontaneous psychological recovery" from the acute cardiac event. In the few randomized, controlled studies reported,[42–44] exercise training had little or no effect on psychosocial functioning.

Stern and Cleary[42,45] reported results from the National Exercise and Heart Disease Project. Six hundred fifty-one men, aged 30 to 64 years, who had at least 1 myocardial infarction 8 weeks to 36 months earlier, completed a 6-week low-level exercise program in which intensity was limited to a maximum of 72% of age-predicted heart rate. Although this initial program was designed, in part, to help identify potential dropouts, it resulted in positive psychosocial, sexual and vocational changes.[45] After the prerandomization phase, compliers were randomly assigned to a moderate to high intensity supervised exercise program 3 days/week or to a nonexercising control group. No differences were noted between the groups at the 6-month, 1- and 2-year follow-up examinations.[42]

Blumenthal et al[46] compared the effects of 12 weeks of moderate to high intensity (65 to 75% $\dot{V}O_2$max) versus low-intensity (<45% $\dot{V}O_2$max) exercise on psychosocial functioning in 70 patients with a recent (<1 year) myocardial infarction. No differences were found between groups in any measure of psychosocial functioning, including anxiety, depression, stress, anger and type A behavior. The investigators suggested that group therapy or stress management may be more effective than exercise in reducing the psychological dysfunction complicating acute myocardial infarction.

Morbidity and mortality: Eight of the major randomized trials of rehabilitation with exercise after myocardial infarction[47–54] (Table III) involved 3,103 patients who were followed for 1 to 9 years. Effectiveness of these interventions, as expressed by the formula: [(control mortality-intervention mortality/control mortality) × 100] showed a beneficial trend toward increased survival (7 of 8 trials), but only one study[51] attained statistical significance. Because these studies were limited by sample size, recent attempts have been made to pool data from similar randomized clinical trials. Two meta-analyses have now shown that cardiac rehabilitation provides a 20 to 25% reduction in total and cardiovascular-related mortality; however, neither report found a significant decrease in the rate of nonfatal recurrent myocardial infarction.[55,56] The exercise dosage administered in these studies was only 50 to 75% $\dot{V}O_2$max for 20 to 60 minutes 2 to 4 times per week, except for 1 of the studies[50] in which daily home exercises were scheduled. Although concomitant life-style changes, enhanced medical surveillance, or both, may have contributed to the survival advantage, the importance of these data is substantial. The reduction in fatal cardiac events after exercise-based cardiac rehabilitation is similar to that demonstrated with other, more expensive therapies including coronary artery bypass surgery and other medical regimens (β blockers, lipid-lowering agents and antihypertensive treatments). Current thrombolytic and revascularization procedures, which markedly decrease early postinfarction mortality,

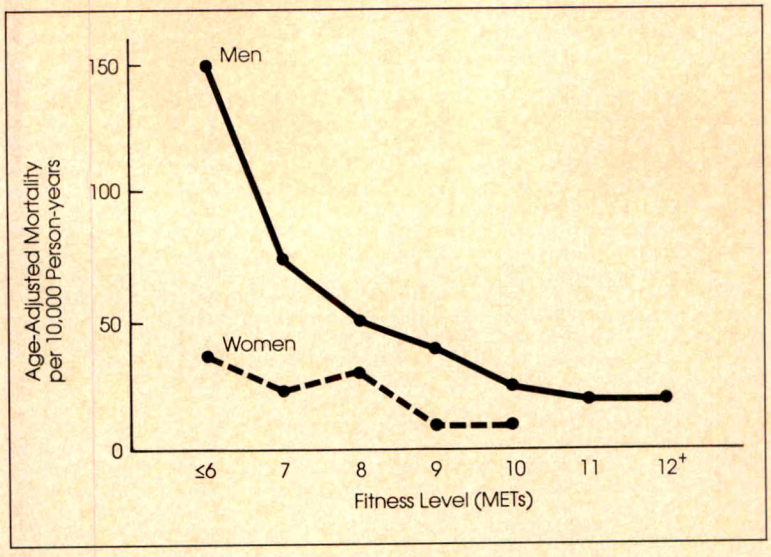


FIGURE 5. Age-adjusted, all-cause mortality rates per 10,000 person-years of follow-up by physical fitness (METs) achieved during maximal treadmill exercise testing. (Adapted from Blair et al.[58])

would likely diminish the impact of adjunctive cardiac rehabilitation programs on survival.[57]

RELATION BETWEEN FITNESS AND ALL-CAUSE MORTALITY: Blair et al[58] identified a low level of aerobic fitness as an independent risk factor for all-cause mortality. The investigators prospectively studied 10,224 men and 3,120 women who were given a preventive medical examination and a maximal treadmill exercise test to assess their $\dot{V}O_2$max. Over an average follow-up of slightly >8 years, 240 men and 43 women died. In general, the higher the initial level of fitness, the lower the subsequent mortality rate from cancer and heart disease (Figure 5), even after statistical adjustments were made for age, coronary risk factors, family history of heart disease, and follow-up interval. However, there appeared to be no additional benefit (i.e., lower mortality) associated with fitness levels higher than 9 METs in women and 10 METs in men. Moreover, the greatest reduction in risk for both men and women occurred with progression from the lowest fitness category (≤6 METs) to the next lowest level (7 METs), suggesting that even a modest improvement in fitness among the most unfit confers a substantial protective benefit. These findings and other recent analyses[2,59] suggest that the optimal amount of energy expenditure for reducing heart disease mortality can be accomplished by a brisk walk of 30 to 70 minutes each day. This is encouraging from a preventive medicine and public health standpoint, since most people should be able to schedule this amount of leisure-time physical activity into their daily routine.

Conclusion: Low to moderate intensity exercise training can produce beneficial changes in functional capacity, cardiac function, coronary risk factors, psychosocial well-being and possibly improve survival in patients with CAD. These findings may be especially relevant for the inactive patient in whom the subjective discomfort of vigorous physical training may serve as a deterrent to long-term compliance with exercise therapy. Unless future studies can show that the added benefits of high-intensity exercise outweigh the potential risks, it appears prudent to recommend more moderate exercise regimens for patients with CAD. We must conclude, as Hippocrates[60] summarized it, that:

> ". . . all parts of the body which have a function, if used in *moderation* and exercised in labours in which each is accustomed, become thereby healthy, well-developed and age more slowly, but if unused and left idle they become liable to disease, defective in growth, and age quickly."

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INTRODUCING

NEW ZOCOR™ ONCE-A-DAY (SIMVASTATIN)



An HMG-CoA reductase inhibitor for a wide range of patients with primary hypercholesterolemia (Types IIa and IIb) as an adjunct to diet

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For many patients
with primary hypercholesterolemia,

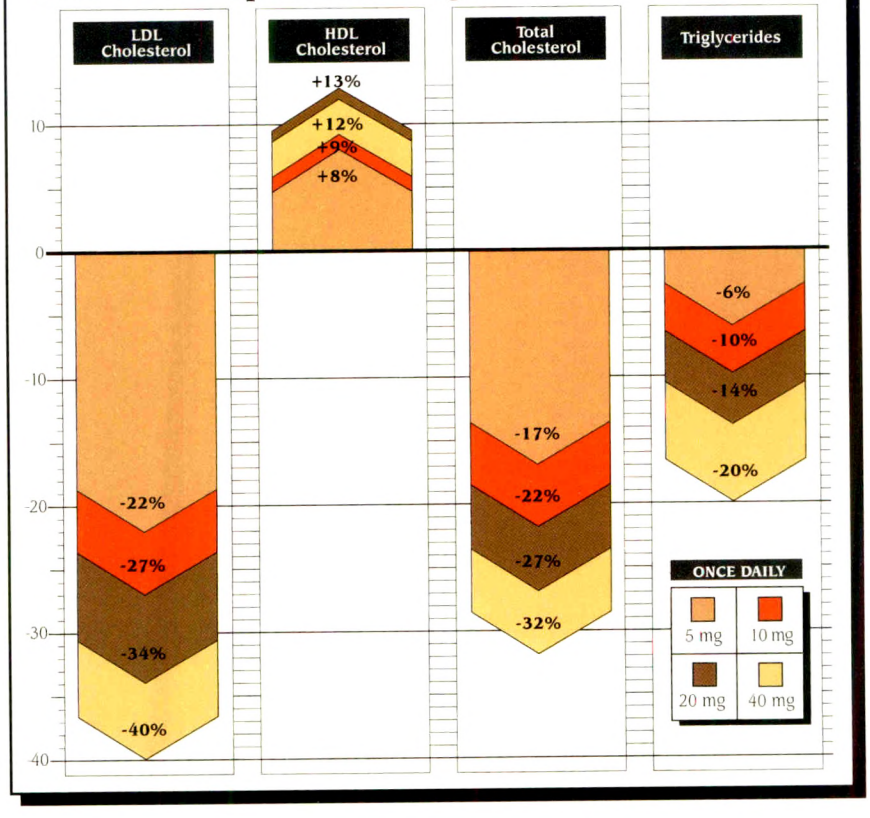
THE EFFICACY THAT YOU NEED

Working to achieve your high standards for lowering cholesterol

In indicated patients,

A positive effect on all key lipid parameters

Overall mean percent changes*,**



* Mean percent changes from baseline from two randomized controlled trials of 6 to 8 weeks' duration in 95 patients receiving ZOCOR 5 mg once daily. In these studies, mean baseline cholesterol levels (on diet) were 209 mg/dL for LDL cholesterol and 288 mg/dL for total cholesterol.

** Mean percent changes from baseline from six randomized controlled trials of 4 to 12 weeks' duration in 767 patients receiving ZOCOR 10, 20, or 40 mg once daily. In these studies, mean baseline cholesterol levels (on diet) were 277 mg/dL for LDL cholesterol and 354 mg/dL for total cholesterol.

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The recommended starting dose is 5 or 10 mg once a day in the evening. Patients with LDL cholesterol levels (on diet) >190 mg/dL should be started on 10 mg once a day. A starting dose of 5 mg once a day should be considered for patients with LDL cholesterol (on diet) of ≤190 mg/dL and for elderly patients. For more information about dosage, including dosage in patients who are on concomitant immunosuppressive therapy or in patients with severe renal insufficiency, see full Prescribing Information.

ZOCOR is contraindicated in patients who are hypersensitive to any component of the medication; in patients with active liver disease or unexplained persistent transaminase elevations (see WARNINGS); in pregnant or lactating patients; and in women of childbearing age except when such patients are highly unlikely to conceive. For additional details, including information about liver function testing and myopathy, see full Prescribing Information.

For a wide range of patients with primary hypercholesterolemia (Types IIa and IIb), after an adequate trial of diet and other nondrug therapy,

NEW ZOCOR™ ONCE-A-DAY (SIMVASTATIN)



ONCE-A-DAY
ZOCOR™
(SIMVASTATIN)

ZOCOR is available in 5-mg, 10-mg, 20-mg, and 40-mg tablet strengths.

CONTRAINDICATIONS: Hypersensitivity to any component of this medication.

Active liver disease or unexplained persistent elevations of serum transaminases (see WARNINGS).

Pregnancy and lactation. Atherosclerosis is a chronic process, and the discontinuation of lipid-lowering drugs during pregnancy should have little impact on the outcome of long-term therapy of primary hypercholesterolemia. Moreover, cholesterol and other products of the cholesterol biosynthesis pathway are essential components for fetal development, including synthesis of steroids and cell membranes. Because of the ability of HMG-CoA reductase inhibitors such as ZOCOR® (Simvastatin) to decrease the synthesis of cholesterol and possibly other products of the cholesterol biosynthesis pathway, ZOCOR may cause fetal harm when administered to a pregnant woman. Therefore, simvastatin is contraindicated during pregnancy and in nursing mothers. **Simvastatin should be administered to women of childbearing age only when such patients are highly unlikely to conceive.** If a patient becomes pregnant while taking this drug, simvastatin should be discontinued and the patient should be apprised of the potential hazard to the fetus.

WARNINGS: ***Liver Dysfunction:*** **Persistent increases (to more than 3 times the upper limit of normal) in serum transaminases have occurred in 1% of patients who received simvastatin in clinical trials.** When drug treatment was interrupted or discontinued in these patients, the transaminase levels usually fell slowly to pretreatment levels. The increases were not associated with jaundice or other clinical signs or symptoms. There was no evidence of hypersensitivity.

It is recommended that liver function tests be performed during therapy with simvastatin. Serum transaminase levels, including ALT (SGPT), should be monitored before treatment begins, every 6 weeks for the first 3 months, every 8 weeks during the remainder of the first year, and periodically thereafter (e.g., at approximately 6-month intervals). Special attention should be paid to patients who develop elevated serum transaminase levels, and in these patients, measurements should be repeated promptly and then performed more frequently. If the transaminase levels show evidence of progression, particularly if they rise to 3 times the upper limit of normal and are persistent, the drug should be discontinued. Liver biopsy should be considered if elevations persist beyond the discontinuation of the drug.

The drug should be used with caution in patients who consume substantial quantities of alcohol and/or have a past history of liver disease. Active liver diseases or unexplained transaminase elevations are contraindications to the use of simvastatin.

As with other lipid-lowering agents, moderate (less than 3 times the upper limit of normal) elevations of serum transaminases have been reported following therapy with simvastatin. These changes appeared soon after initiation of therapy with simvastatin, were often transient, were not accompanied by any symptoms, and did not require interruption of treatment.

Skeletal Muscle: Rare cases of rhabdomyolysis with acute renal failure secondary to myoglobinuria have been associated with simvastatin therapy. Rhabdomyolysis has also been associated with other HMG-CoA reductase inhibitors when they were administered alone or concomitantly with 1) immunosuppressive therapy, including cyclosporine in cardiac transplant patients; 2) gemfibrozil or lipid-lowering doses (≥1 g/day) of nicotinic acid in non-transplant patients; or 3) erythromycin in seriously ill patients. Some of the patients who had rhabdomyolysis in association with the reductase inhibitors had preexisting renal insufficiency, usually as a consequence of longstanding diabetes. In most subjects who have had an unsatisfactory lipid response to either simvastatin or gemfibrozil alone, the possible benefits of combined therapy with these drugs are not considered to outweigh the risk of severe myopathy, rhabdomyolysis, and acute renal failure. While it is not known whether this interaction occurs with fibrates other than gemfibrozil, myopathy and rhabdomyolysis have occasionally been associated with the use of other fibrates alone, including clofibrate. Therefore, the combined use of simvastatin with other fibrates should generally be avoided.

Physicians contemplating combined therapy with simvastatin and lipid-lowering doses of nicotinic acid or with immunosuppressive drugs should carefully weigh the potential benefits and risks and should carefully monitor patients for any signs or symptoms of muscle pain, tenderness, or weakness, particularly during the initial months of therapy and during any periods of upward dosage titration of either drug. Periodic creatine phosphokinase (CPK) determinations may be considered in such situations, but there is no assurance that such monitoring will prevent the occurrence of severe myopathy.

Because of an apparent relationship between myopathy and increased plasma levels of active metabolites derived from other HMG-CoA reductase inhibitors, the daily dosage should not exceed 10 mg/day in patients who are taking cyclosporine (see DOSAGE AND ADMINISTRATION in Prescribing Information).

Simvastatin therapy should be temporarily withheld or discontinued in any patient who has an acute, serious condition suggestive of a myopathy or who has a risk factor predisposing to the development of renal failure secondary to rhabdomyolysis (e.g., severe acute infection, hypotension, major surgery, trauma, severe metabolic, endocrine, and electrolyte disorders, and uncontrolled seizures).

Myopathy should be considered in any patient with diffuse myalgias, muscle tenderness or weakness, and/or marked elevation of CPK. Patients should be advised to report promptly unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever. Simvastatin therapy should be discontinued if markedly elevated CPK levels occur or if myopathy is diagnosed or suspected.

PRECAUTIONS: ***General:*** Before instituting therapy with ZOCOR, an attempt should be made to control hypercholesterolemia with appropriate diet, exercise, and weight reduction in obese patients and to treat other underlying medical problems (see INDICATIONS AND USAGE in Prescribing Information).

Simvastatin may cause elevation of CPK and transaminase levels (see WARNINGS and ADVERSE REACTIONS). This should be considered in the differential diagnosis of chest pain in a patient on therapy with simvastatin.

Homozygous Familial Hypercholesterolemia: ZOCOR is less effective in patients with the rare homozygous familial hypercholesterolemia, possibly because these patients have few functional LDL receptors.

Information for Patients: Patients should be advised to report promptly unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever.

Drug Interactions: *Immunosuppressive Drugs, Gemfibrozil, Niacin (Nicotinic Acid), Erythromycin:* See WARNINGS, *Skeletal Muscle.*

Antipyrine: Because simvastatin had no effect on the pharmacokinetics of antipyrine, interactions with other drugs metabolized via the same cytochrome isozymes are not expected.

Propranolol: In healthy male volunteers, there was a significant decrease in mean C_{max}, but no change in AUC, for simvastatin total and active inhibitors with concomitant administration of single doses of ZOCOR® (Simvastatin) and propranolol. The clinical relevance of this finding is unclear. The pharmacokinetics of the enantiomers of propranolol were not affected.

Digoxin: Concomitant administration of a single dose of digoxin in healthy male volunteers receiving simvastatin resulted in a slight elevation (less than 0.3 ng/mL) in digoxin concentrations in plasma (as measured by a radioimmunoassay) compared to concomitant administration of placebo and digoxin. Patients taking digoxin should be monitored appropriately when simvastatin is initiated.

Warfarin: Simvastatin therapy appeared to enhance slightly the anticoagulant effect of warfarin (mean changes in prothrombin time less than 2 seconds) in normal volunteers maintained in a state of low therapeutic anticoagulation. With other reductase inhibitors, clinically evident bleeding and/or increased prothrombin time has been reported in a few patients taking coumarin anticoagulants concomitantly. In such patients, prothrombin time should be determined before starting simvastatin and frequently enough during early therapy to insure that no significant alteration of prothrombin time occurs. Once a stable prothrombin time has been documented, prothrombin times can be monitored at the intervals usually recommended for patients on coumarin anticoagulants. If the dose of simvastatin is changed, the same procedure should be repeated. Simvastatin therapy has not been associated with bleeding or with changes in prothrombin time in patients not taking anticoagulants.

Other Concomitant Therapy: Although specific interaction studies were not performed, in clinical studies, simvastatin was used concomitantly with angiotensin-converting-enzyme (ACE) inhibitors, beta blockers, calcium channel blockers, diuretics, and nonsteroidal anti-inflammatory drugs (NSAIDs) without evidence of clinically significant adverse interactions. The effect of cholestyramine on the absorption and kinetics of simvastatin has not been determined.

Endocrine Function: HMG-CoA reductase inhibitors interfere with cholesterol synthesis and as such might theoretically blunt adrenal and/or gonadal steroid production. However, clinical studies have shown that simvastatin does not reduce basal plasma cortisol concentration or impair adrenal reserve and does not reduce basal plasma testosterone concentration (see CLINICAL PHARMACOLOGY, *Clinical Studies* in Prescribing Information). Another HMG-CoA reductase inhibitor has been shown to reduce the plasma testosterone response to HCG; the effect of simvastatin on HCG-stimulated testosterone secretion has not been studied.

Results of clinical trials with drugs in this class have been inconsistent with regard to drug effects on basal and reserve steroid levels. The effects of HMG-CoA reductase inhibitors on male fertility have not been studied in adequate numbers of male patients. The effects, if any, on the pituitary-gonadal axis in pre-menopausal women are unknown. Patients treated with simvastatin who develop clinical evidence of endocrine dysfunction should be evaluated appropriately. Caution should also be exercised if an HMG-CoA reductase inhibitor or other agent used to lower cholesterol levels is administered to patients who are also receiving other drugs (e.g., ketoconazole, spironolactone, cimetidine) that may decrease the levels or activity of endogenous steroid hormones.

CNS Toxicity: Optic nerve degeneration was seen in clinically normal dogs treated with simvastatin for 14 weeks at 180 mg/kg/day, a dose that produced mean plasma drug levels about 44 times higher than the mean drug level in humans taking 40 mg/day.

CNS vascular lesions, characterized by perivascular hemorrhage and edema, mononuclear cell infiltration of perivascular spaces, perivascular fibrin deposits, and necrosis of small vessels, were seen in dogs treated with simvastatin at a dose of 360 mg/kg/day, a dose that produced plasma drug levels that were about 50 times higher than the mean drug levels in humans taking 40 mg/day. Similar CNS vascular lesions have been observed with several other drugs of this class.

A chemically similar drug in this class also produced optic nerve degeneration (Wallerian degeneration of retinogeniculate fibers) in clinically normal dogs in a dose-dependent fashion starting at 60 mg/kg/day, a dose that produced mean plasma drug levels about 30 times higher than the mean drug level in humans taking the highest recommended dose (as measured by total enzyme inhibitory activity). This same drug also produced vestibulocochlear Wallerian-like degeneration and retinal ganglion cell chromatolysis in dogs treated for 14 weeks at 180 mg/kg/day, a dose that resulted in a mean plasma drug level similar to that seen with the 60 mg/kg/day dose.

Carcinogenesis, Mutagenesis, Impairment of Fertility: In a 72-week carcinogenicity study, mice were administered daily doses of simvastatin of 25, 100, and 400 mg/kg body weight, which resulted in mean plasma drug levels approximately 3, 15, and 33 times higher than the mean human plasma drug concentration (as total inhibitory activity) after a 40-mg oral dose. Liver carcinomas were significantly increased in high-dose females and in mid- and high-dose males, with a maximum incidence of 90% in males. The incidence of adenomas of the liver was significantly increased in mid- and high-dose females. Drug treatment also significantly increased the incidence of lung adenomas in mid- and high-dose males and females. Adenomas of the Harderian gland (a gland of the eye of rodents) were significantly higher in high-dose mice than in controls. No evidence of a tumorigenic effect was observed at 25 mg/kg/day. Although mice were given up to 500 times the human dose (HD) on a mg/kg body weight basis, blood levels of HMG-CoA reductase inhibitory activity were only 3 to 33 times higher in mice than in humans given 40 mg of ZOCOR.

In a separate 92-week carcinogenicity study in mice at doses of up to 25 mg/kg/day, no evidence of a tumorigenic effect was observed. Although mice were given up to 31 times the human dose on a mg/kg basis, plasma drug levels were only 2 to 4 times higher than in humans given 40 mg simvastatin as measured by AUC.

In a 2-year study in rats, there was a statistically significant increase in the incidence of thyroid follicular adenomas in female rats exposed to approximately 45 times higher levels of simvastatin than humans given 40 mg simvastatin (as measured by AUC). Preliminary results from a second 2-year rat study indicate an increase in the incidence of thyroid and liver tumors in male and female rats at doses that produce exposure levels ≥29 times (based on AUC) those achieved in humans at a dosage of 40 mg/day. Liver tumors are found in rodents with all the chemically similar drugs of this class. No increased incidence of tumors was observed at doses that produce exposure levels 15 times (based on AUC) those seen in man.

No evidence of mutagenicity was observed in a microbial mutagen test using mutant strains of *Salmonella typhimurium* with or without rat or mouse liver metabolic activation. In addition, no evidence of damage to genetic material was noted in an *in vitro* alkaline elution assay using rat hepatocytes, a V-79 mammalian cell forward mutation study, an *in vitro* chromosome aberration study in CHO cells, or an *in vivo* chromosomal aberration assay in mouse bone marrow.

There was decreased fertility in male rats treated with simvastatin for 34 weeks at 25 mg/kg body weight (15 times the maximum human exposure level, based on AUC, in patients receiving 40 mg/day); however, this effect was not observed during a subsequent fertility study in which simvastatin was administered at this same dose level to male rats for 11 weeks (the entire cycle of spermatogenesis including epididymal maturation). No microscopic changes were observed in the testes of rats from either study. At 180 mg/kg/day (which produces exposure levels 44 times higher than those in humans taking 40 mg/day), seminiferous tubule degeneration (necrosis and loss of spermatogenic epithelium) was observed. In dogs, there was drug-related testicular atrophy, decreased spermatogenesis, spermatocytic degeneration, and giant cell formation at 10 mg/kg/day (approximately 7 times the human exposure level, based on AUC, at 40 mg/day). The clinical significance of these findings is unclear.

Pregnancy: *Pregnancy Category X.* See CONTRAINDICATIONS.

Safety in pregnant women has not been established. Simvastatin was not teratogenic in rats at doses of 25 mg/kg/day or in rabbits at doses of up to 10 mg/kg daily. These doses resulted in 6 times (rat) or 4 times (rabbit) the human exposure based on mg/m² surface area. However, in studies with another structurally related HMG-CoA reductase inhibitor, skeletal malformations were observed in rats and mice. Simvastatin should be administered to women of childbearing potential only when such patients are highly unlikely to conceive and have been informed of the potential hazards. If a woman becomes pregnant while taking simvastatin, it should be discontinued and the patient should be advised again as to the potential hazards to the fetus.

Nursing Mothers: It is not known whether simvastatin is excreted in human milk. Because a small amount of another drug in this class is excreted in human milk and because of the potential for serious adverse reactions in nursing infants, women taking simvastatin should not nurse their infants (see CONTRAINDICATIONS).

Pediatric Use: Safety and effectiveness in children and adolescents have not been established. Because children and adolescents are not likely to benefit from cholesterol lowering for at least a decade and because experience with this drug is limited (no studies in subjects below the age of 20 years), treatment of children or adolescents with simvastatin is not recommended at this time.

ADVERSE REACTIONS: In the controlled clinical studies and their open extensions (2,423 patients with mean duration of follow-up of approximately 18 months), 1.4% of patients were discontinued due to adverse experiences attributable to ZOCOR® (Simvastatin). Adverse reactions have usually been mild and transient. ZOCOR has been evaluated for serious adverse reactions in more than 21,000 patients and is generally well tolerated.

Clinical Adverse Experiences: Adverse experiences occurring at an incidence of 1% or greater in patients treated with ZOCOR, regardless of causality, in controlled clinical studies are shown in the table below:

	ZOCOR (N=1,583)	Placebo (N=157)	Cholestyramine (N=179)	Probucol (N=81)
Body as a Whole				
Abdominal pain	3.2%	3.2%	8.9%	2.5%
Asthenia	1.6	2.5	1.1	1.2
Gastrointestinal				
Constipation	2.3	1.3	29.1	1.2
Diarrhea	1.9	2.5	7.8	3.7
Dyspepsia	1.1	—	4.5	3.7
Flatulence	1.9	1.3	14.5	6.2
Nausea	1.3	1.9	10.1	2.5
Nervous System/Psychiatric				
Headache	3.5	5.1	4.5	3.7
Respiratory				
Upper respiratory infection	2.1	1.9	3.4	6.2

The following effects have been reported with drugs in this class:

Skeletal: Myopathy, rhabdomyolysis, arthralgias.

Neurological: Dysfunction of certain cranial nerves (including alteration of taste, impairment of extraocular movement, facial paresis), tremor, vertigo, memory loss, paresthesia, peripheral neuropathy, peripheral nerve palsy, anxiety, insomnia, depression.

Hypersensitivity Reactions: An apparent hypersensitivity syndrome has been reported rarely which has included one or more of the following features: anaphylaxis, angioedema, lupus erythematous-like syndrome, polymyalgia rheumatica, vasculitis, purpura, thrombocytopenia, leukopenia, hemolytic anemia, positive ANA, ESR increase, arthritis, arthralgia, urticaria, asthenia, photosensitivity, fever, chills, flushing, malaise, dyspnea, toxic epidermal necrolysis, erythema multiforme, including Stevens-Johnson syndrome.

Gastrointestinal: Pancreatitis; hepatitis, including chronic active hepatitis, cholestatic jaundice, fatty change in liver, and, rarely, cirrhosis, fulminant hepatic necrosis, and hepatoma; anorexia; vomiting.

Skin: Alopecia.

Reproductive: Gynecomastia, loss of libido, erectile dysfunction.

Eye: Progression of cataracts (lens opacities), ophthalmoplegia.

Laboratory Abnormalities: Elevated transaminases, alkaline phosphatase, and bilirubin; thyroid function abnormalities.

Laboratory Tests: Marked persistent increases of serum transaminases have been noted (see WARNINGS, *Liver Dysfunction*). About 5% of patients had elevations of CPK levels of 3 or more times the normal value on one or more occasions. This was attributable to the noncardiac fraction of CPK. Muscle pain or dysfunction usually was not reported (see WARNINGS, *Skeletal Muscle*).

Concomitant Therapy: In controlled clinical studies in which simvastatin was administered concomitantly with cholestyramine, no adverse reactions peculiar to this concomitant treatment were observed. The adverse reactions that occurred were limited to those reported previously with simvastatin or cholestyramine. The combined use of simvastatin with fibrates should generally be avoided (see WARNINGS, *Skeletal Muscle*).

OVERDOSAGE: Significant lethality was observed in mice after a single oral dose of 9 g/m². No evidence of lethality was observed in rats or dogs treated with doses of 30 and 100 g/m², respectively. No specific diagnostic signs were observed in rodents. At these doses, the only signs seen in dogs were emesis and mucoid stools.

There have been no cases of clinically significant overdosage with ZOCOR in humans. Until further experience is obtained, no specific treatment of overdosage with ZOCOR can be recommended.

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Effect of Direct, Reflex and Exercise-Provoked Increases in Sympathetic Tone on Idiopathic Ventricular Tachycardia

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Exercise treadmill testing and direct enhancement of sympathetic influence with agents such as isoproterenol are often used to reproduce ventricular tachycardia (VT). The cardiac effects of, and arrhythmia responses to, graded exercise, isoproterenol infusion and lower body negative pressure (the latter 2 with and without atrial and ventricular stimulation) were studied in 11 patients with idiopathic VT. During maximal exercise, substantial increases in heart rate and blood pressure occurred, but only 2 of 9 exercised patients had VT (during recovery in both). During programmed stimulation alone, VT was initiated in 6 patients. During maximum levels of lower body negative pressure (−60 cm of water in most), mean systolic blood pressure decreased by 10 mm Hg, heart rate increased by 15 beats/min, and ventricular refractory period decreased by 10 ms. In 4 patients VT occurred spontaneously during lower body negative pressure; in 2, lower body negative pressure was the only intervention producing VT. During isoproterenol infusion VT occurred spontaneously in 2 patients; both had VT initiated during other interventions. Lower body negative pressure and isoproterenol increased VT rate, but did not prolong it. It is concluded that there is significant variability in arrhythmia responses to sympathetic augmentation, suggesting that additional covariables such as parasympathetic input and ventricular volume may also have a role in arrhythmia occurrence.

(Am J Cardiol 1992;69:1433–1438)

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Beta-adrenergic influences affect both heart rate and ventricular effective refractory period in both experimental animals[1] and humans,[2–4] and have an important role in cardiac arrhythmias, regardless of basic mechanism. Studies of β-adrenergic influence on cardiac arrhythmias in humans have largely been limited to observations during exercise, a complex stimulus, or infusion of arbitrary doses of isoproterenol or epinephrine.[2,3,5] Previous studies showed that orthostatic stress as provided by lower body negative pressure increases heart rate and decreases the right ventricular effective refractory period.[4]

The goal of the current study was to compare the electrophysiologic responses to exercise, isoproterenol and lower body negative pressure, and the influence of each on ventricular tachycardia (VT) induction and characteristics in a group of patients with idiopathic VT.

METHODS

Patient selection: Patients were identified from a group referred for electrophysiologic evaluation of VT. Selection was based on the presence of ≥1 clinical feature or characteristic of spontaneous VT that has been used to describe patients with idiopathic VT.[6–10] Eleven patients were identified for study based on the aforementioned criteria. The clinical and VT characteristics of each patient are listed in Table I. In general, patients had little or no evidence of heart disease; 3 had evidence of mild heart disease with preserved left ventricular function (such as echocardiographic mitral valvular prolapse, cardiomyopathy and a wall motion abnormality with angiographically normal coronaries).

Study protocol: EXERCISE TESTING: Exercise treadmill testing using the Bruce protocol[11] was performed in 9 of 11 patients; in 2 testing was not performed, because of orthopedic problems or at the patient's request. In several patients, exercise testing was performed before referral. In all cases, the end point of testing was exhaustion or the initiation of VT.

ELECTROPHYSIOLOGIC TESTING: All patients underwent programmed stimulation in the nonsedated, fasting state in the absence of cardioactive medications. After local lidocaine anesthesia (1 to 2 ml of 1% solution), 2 quadripolar electrode catheters were inserted in the femoral vein using the Seldinger technique and advanced to the heart under fluoroscopic guidance. The clinical study was then performed using previously reported techniques of programmed stimulation.[2] To minimize variability of effective refractory period measurement, we routinely use stimulation outputs likely to be

TABLE I Clinical Characteristics of the Study Population

Patient	Age (yr) & Sex	Heart Disease	VT QRS (BB/axis)	VT Cycle Length (ms)	VT Duration
1	46M	0	LBBB/inf	320	NS
2	71F	0		280	NS
3	71M	0	LBBB/inf	380	NS
4	43F	0	LBBB/inf	360	NS
5	21F	MVP	LBBB/inf	320	S & NS
6	67M	Mild CM	RBBB/inf	300	NS
7	47F	IWMA	RBBB/sup	280	NS
8	39F	0	LBBB/inf	360	NS
9	40F	0	LBBB/inf	320	S
10	30F	0	LBBB/inf	360	S
11	33F	0	LBBB/inf	290	NS

CM = cardiomyopathy; inf = inferior; IWMA = inferior wall motion abnormality; LBBB = left bundle branch block pattern; NS = nonsustained; RBBB = right bundle branch block pattern; sup = superior; S = sustained; VT = ventricular tachycardia.

on the steep portion of the strength-interval curve, of 2 ms in pulse width and at an amplitude of 4 times the late diastolic threshold.[12] Before subsequent interventions were performed, incremental atrial pacing (to atrioventricular nodal block), atrial extrastimuli, incremental ventricular pacing, and single- and double-ventricular extrastimuli during ventricular drive (usually cycle lengths of 600 and 450 ms at right ventricular apex) were used. The right ventricular apex was used for study because of the superior stability of the site during lower body negative pressure studies. For the purpose of this study we defined VT as ≥3 consecutive induced or spontaneous ventricular complexes with a rate >100 beats/min. Nonsustained VT was arbitrarily defined as lasting <30 seconds before stopping spontaneously. Sustained VT lasted >30 seconds.

LOWER BODY NEGATIVE PRESSURE TESTING: We used a technique for lower body negative pressure during electrophysiologic testing, which was previously reported.[4] Heart rate, systolic blood pressure (automated inflating cuff technique), right ventricular apex effective refractory period and response to atrial overdrive, ventricular overdrive, and single- and double-ventricular extrastimuli (pacing cycle length 450 ms) were determined after 3 to 5 minutes of lower body negative pressure at levels of 0, −20, −40 and −60 cm of water. End points of testing were VT induction and intolerance to incremental levels of lower body negative pressure. No complications were observed during testing.

ISOPROTERENOL TESTING: After completion of the protocol, at a time when heart rate, systolic blood pressure and effective refractory period had returned to baseline values, isoproterenol was infused intravenously in 8 of 11 patients at a rate sufficient to achieve the maximum heart rate observed during lower body negative pressure. Isoproterenol testing was declined in 3 patients due to the additional time requirements. After 3 to 5 minutes at the desired infusion rate, heart rate, systolic blood pressure and effective refractory period were determined, as well as response to atrial and ventricular overdrive pacing, and to single and double extrastimuli during ventricular pacing at a cycle length of 450 ms.

Data analysis: Data reported for lower body negative pressure periods represent measurements obtained during the most negative pressure achieved in each patient; 8 patients underwent study to levels of −60, two to −40, and one to −35 cm of water. The procedure was well-tolerated in all patients. VT was considered reproducibly observed if the clinical electrocardiographic morphology was produced at least twice during any experimental condition (baseline control, lower body negative pressure, or isoproterenol alone or in combination with atrial or ventricular pacing protocols). VT duration is reported as the maximum number of complexes observed during each experimental condition (as aforementioned). VT cycle length is reported as the average of VT runs recorded during each experimental period. Only similar VT morphologies were compared. Data are expressed as mean ± SD, where appropriate. Paired *t* tests were used to statistically compare responses to interventions.

RESULTS

Hemodynamic and electrophysiologic responses to interventions: EXERCISE TESTING: As expected, this patient group as a whole exhibited little functional impairment on exercise treadmill testing. Upright heart rate increased from a baseline value of 80 ± 7 beats/min to a maximum of 154 ± 8 beats/min, which represented an increase of 83 ± 13% of predicted maximum heart rate. Upright systolic blood pressure was 107 ± 4 mm Hg at rest and was 146 ± 7 mm Hg at peak exercise. No ischemic changes were noted during testing.

LOWER BODY NEGATIVE PRESSURE TESTING: Systolic blood pressure, heart rate and effective refractory period responses to maximum achievable levels of lower body negative pressure are shown in Figure 1 and as individual responses in Table II. Blood pressure decreased approximately 10 mm Hg, and heart rate increased by 15 beats/min, a result similar to that previously reported.[4] In response to the hemodynamic perturbation, the ventricular effective refractory period decreased by just over 10 ms, as we previously noted in other patients.

ISOPROTERENOL TESTING: Blood pressure, heart rate and effective refractory period responses to infused isoproterenol are also shown in Figure 1. The average lower body negative pressure and isoproterenol heart rate responses in 8 patients undergoing both interventions did not differ by design. The resulting blood pressure and effective refractory period responses to infused isoproterenol were approximately equivalent to those noted during lower body negative pressure and did not differ statistically.

Arrhythmia responses to testing: Individual patient responses to interventions are listed in Table II. There is considerable variability of response in this group of patients (Table II). Several patients had no VT reproduced with any intervention, whereas in others VT was observed in response to ≥1 intervention. If summarized by intervention, during the period of baseline programmed stimulation, no patient had recurrent spontaneous VT, and 6 had reproduction of clinical VT. During lower body negative pressure, 4 patients had spontaneous VT, and 3 had VT with pacing. Examples of 2 of 3 of the patients with spontaneous VT during

TABLE II Individual Responses to Testing

Patient No.	Programmed Stimulation VT	Exercise ΔHR	Exercise ΔBP	Exercise VT	LBNP Level (cm H_2O)	LBNP ΔHR	LBNP ΔBP	LBNP ΔERP	LBNP VT	Isoproterenol ΔHR	Isoproterenol ΔBP	Isoproterenol ΔERP	Isoproterenol VT
1	0	48	25	0	−35	−1	−32	−10	Sp(13)	38	−14	−10	0
2	0	40	40	0	−40	7	10	−15	0	11	8	−20	0
3	V1, V1(9)	98	15	0	−60	7	0	—	Sp(41)	—	—	—	—
4	V1, V2, V3(24)	56	55	0	−60	14	−5	−10	V1V2V3(13)	39	−16	−20	Sp(18)
5	V1, V2, V3(VT-S)	110	45	0	−40	6	0	−5	V1V2(VT-S)	—	—	—	—
6	V1, V2, V3(18)	—	—	—	−60	24	−28	−20	V1V2(15)	—	—	—	—
7	V1, V2, V3(9)	60	20	0	−60	24	−6	−5	Sp(6)	18	—	−15	Sp(4)
8	V1, V1(4)	98	40	Yes (VT-S)	−60	24	−2	−10	0	24	−28	−5	0
9	0	78	66	Yes (VT-S)	−60	16	9	−25	0	21	18	−5	0
10	0	75	45	0	−60	21	−14	−5	0	17	−10	−15	0
11	0	—	—	—	−60	51	−24	−20	Sp(4)	57	—	—	0

ΔBP = change in systolic blood pressure (mm Hg); ΔERP = change in right ventricular effective refractory period (ms); ΔHR = change in heart rate; LBNP = maximum level of lower body negative pressure; Sp = spontaneously occurring; VT = ventricular tachycardia during intervention; V1V1 = constant cycle ventricular pacing; V1V2 = ventricular pacing with 1 premature; V1V2V3 = ventricular pacing with 2 prematures.

lower body negative pressure alone are shown in Figures 2 and 3. In the first patient (patient 3, Figure 2), any intervention resulting in a heart rate increase was associated with VT initiation, including ventricular overdrive pacing, lower body negative pressure and intravenous atropine. In the second example (patient 1, Figure 3), no such heart rate response was necessary; at a less than maximal level of lower body negative pressure (20 cm of water) VT could be reversibly produced without any change in blood pressure or heart rate.

Of the 7 patients who received isoproterenol infusion, 2 had spontaneous clinical VT during the infusion, and 1 needed additional pacing for VT induction. The remaining 4 patients had no VT observed with these interventions.

Despite considerable heart rate and blood pressure evidence of sympathetic activation (as noted previously), exercise was a weak stimulus to VT in this group of patients. Only 2 of 9 patients undergoing exercise testing had VT during the test; in both cases VT was observed early in the recovery period.

Neither lower body negative pressure nor isoproterenol exerted a significant effect on VT duration in the 6 patients whose VT was provocable during baseline pro-

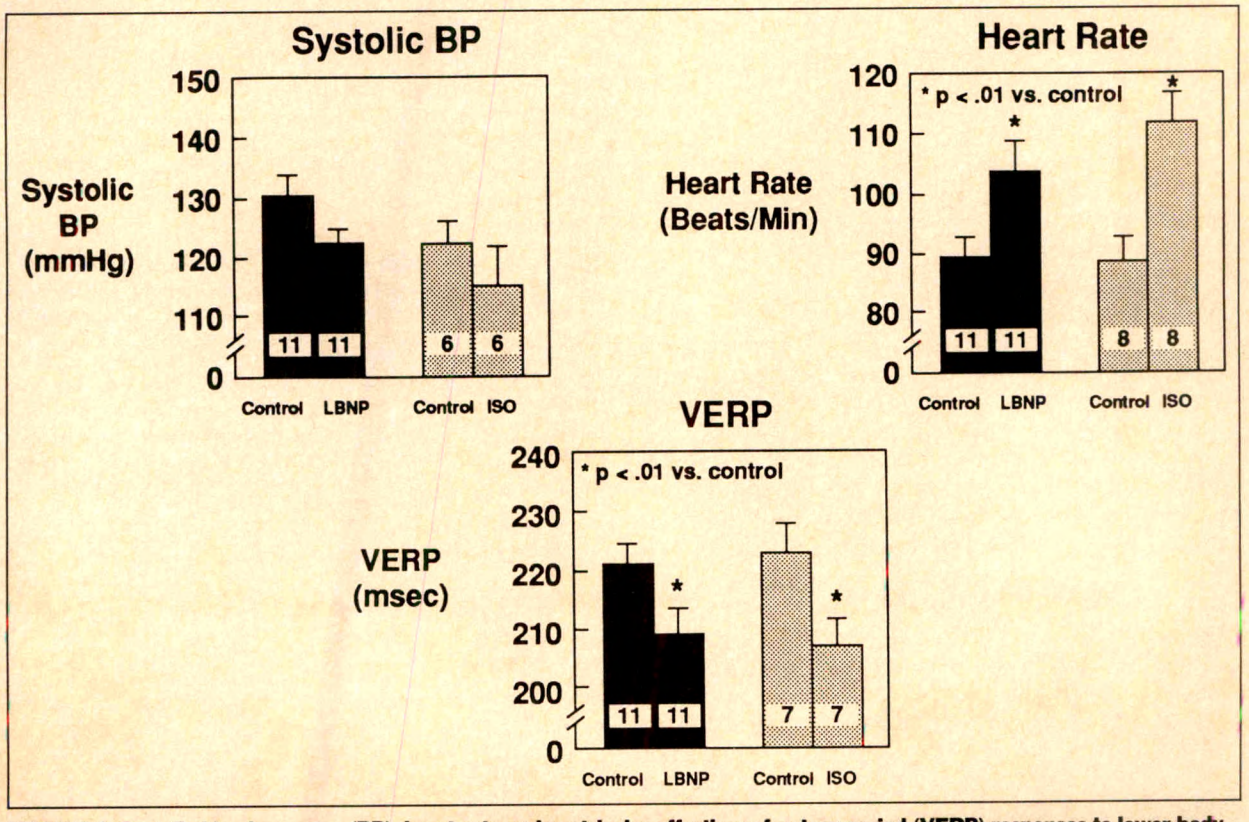


FIGURE 1. Systolic blood pressure (BP), heart rate and ventricular effective refractory period (VERP) responses to lower body negative pressure (LBNP) and isoproterenol (ISO). Numbers within *bars* indicate numbers of patient measurements. Statistics are paired *t* test.

grammed stimulation. In contrast, both lower body negative pressure and isoproterenol shortened VT cycle length compared with that in VT observed clinically or with programmed stimulation alone (Figure 4).

DISCUSSION

A prominent feature of VT occurring in patients without coronary disease is an apparent modulation by adrenergic influences.[6–10,13–15] However, this adrenergic dependence does not implicate any specific electrophysiologic mechanism of VT; it is expected that reentry, abnormal automaticity or triggered activity may all be enhanced in the presence of altered adrenergic influence. The multiplicity of possible mechanisms is reflected in the several distinct clinical subgroups of VT, which have been recognized in patients with little or no heart disease.

Whereas adrenergic influence is a characteristic of patients with idiopathic VT as a group, there is considerable variability between patients in the specific stimulus responsible for arrhythmia occurrence. Dynamic exercise (as represented by exercise treadmill testing) is a complex stimulus of several components.[16] During the recovery phase of exercise, dynamic changes occur both in parasympathetic and sympathetic levels, creating combinations of each that may be unique. It is of interest that when VT occurred in this and previous studies, it was most frequent during the recovery period, rather than early or during peak exercise.

Isoproterenol infusion is the most frequently studied adrenergic intervention used during electrophysiologic testing. It is not completely clear in all cases how isoproterenol facilitates arrhythmia induction. For example, in some idiopathic VT patients, isoproterenol facilitates induction by programmed stimulation without closer coupling intervals at the site of stimulation.[2] In these previously reported patients, isoproterenol may be exerting an effect on intervening tissue[17] between the site of stimulation and the arrhythmia locus (mediated by shortened refractoriness), or a specific effect on the tissue responsible for the arrhythmia. Of 8 patients currently reported, only 2 had spontaneous VT during isoproterenol infusion. Although effective refractory periods shortened in all cases, both patients with VT developed brief spontaneous episodes in the setting of increased heart rate and decreased blood pressure.

We have used lower body negative pressure to activate reflexes originating from cardiac (low levels of negative pressure) and sinoaortic (higher levels) receptors.[18] Previous studies from our laboratory[4] showed

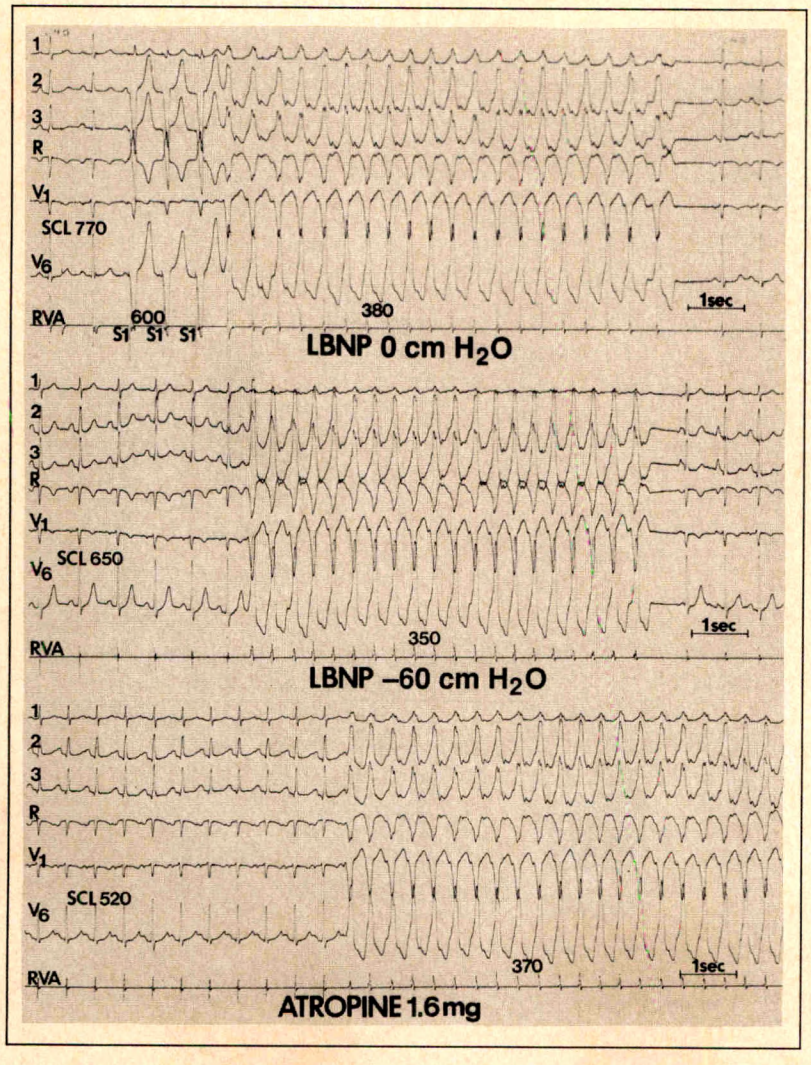


FIGURE 2. Responses to pacing *(top)*, lower body negative pressure (LBNP, *middle*) and atropine *(bottom)*. *All panels* display electrocardiographic leads 1, 2, 3, R, V_1 and V_6, and electrograms from right ventricular apex (RVA). Any intervention resulting in shortening of sinus cycle length (SCL) produced ventricular tachycardia. Note effect of lower body negative pressure on cycle length of ventricular tachycardia.

that lower body negative pressure shortens right ventricular effective refractory period by sympathetic activation at high levels of lower body negative pressure associated with relative arterial hypotension. In contrast, heart rate increases appear to reflect both vagal withdrawal and sympathetic activation. When heart rate is increased to similar levels by 2 different mechanisms (direct [isoproterenol] vs reflex-mediated sympathetic augmentation [lower body negative pressure]), ventricular refractory period responses are identical. This observation supports the notion that parasympathetic withdrawal in ventricular tissues is not an important modulator of ventricular recovery.

The factor responsible for VT occurrence was not uniform in the patients who had facilitation during orthostatic stress. Inspection of individual responses shows that spontaneous VT occurred with and without increased heart rate and reduced blood pressure, and with varying degrees of effective refractory period shortening (Table II). However, even small amounts of lower body

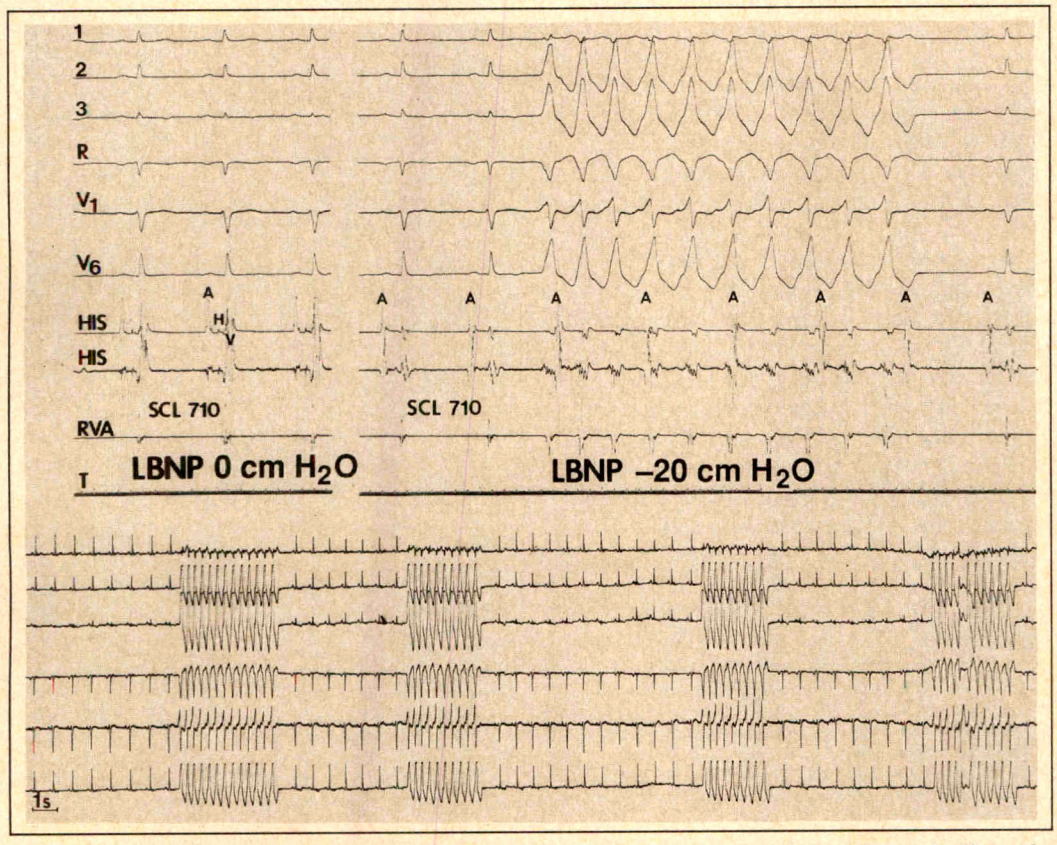


FIGURE 3. Response to low levels of lower body negative pressure (LBNP). *Two top panels* are set up as in Figure 2, except His bundle electrogram is also shown. *Bottom panel,* only surface electrocardiographic leads are displayed. At LBNP of 0 cm of water (H_2O), no ventricular tachycardia was observed. At LBNP of −20 cm of water, at a time when no heart rate changes were noted, ventricular tachycardia was produced in typical repeating pattern *(below)* until LBNP was stopped. RVA = right ventricular apex; SCL = sinus cycle length.

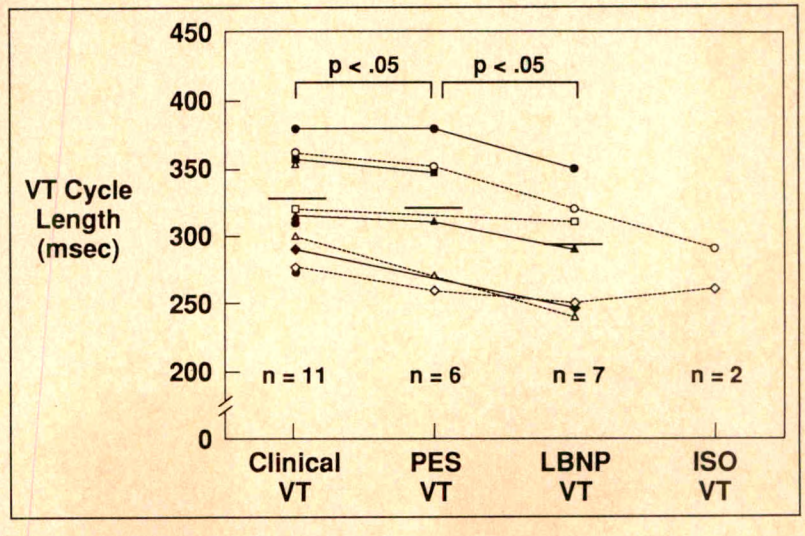


FIGURE 4. Ventricular tachycardia (VT) cycle length on ambulatory electrocardiographic monitoring (Clinical) and in response to programmed stimulation (PES), lower body negative pressure (LBNP) and isoproterenol (ISO). Statistics are paired *t* test.

negative pressure have been shown to significantly increase sympathetic activity, even without apparent heart rate or blood pressure changes.[19] Additional studies will be necessary to substantiate which specific responses to orthostatic stress are responsible for the observed arrhythmia occurrence. Likewise, the factors involved in the absence of a concordant response to β-adrenergic stimulation need clarification.

Study limitations: There are several limitations of this study. First, the clinical behavior of these types of VT (especially repetitive forms) makes assessment of interventions somewhat difficult. However, in each case we were able to compare responses to interventions with control periods during which arrhythmias were quiescent. Whether lower body negative pressure will have more substantial effects in other patients with VT (such as coronary disease) remains to be shown. Second, underestimation of arrhythmia facilitation during isoproterenol infusion may have occurred, because doses were limited by study design (although the heart rate and associated refractory period responses we achieved were similar to other studies). Whereas all patients underwent complete ventricular stimulation, only 1 right ventricular site (apex) was studied owing to physical constraints of the lower body negative pressure protocol. Finally, the efficacy of exercise treadmill testing may have been underestimated, because the study was performed only once; the poor reproducibility of exercise testing for arrhythmia detection is well known.

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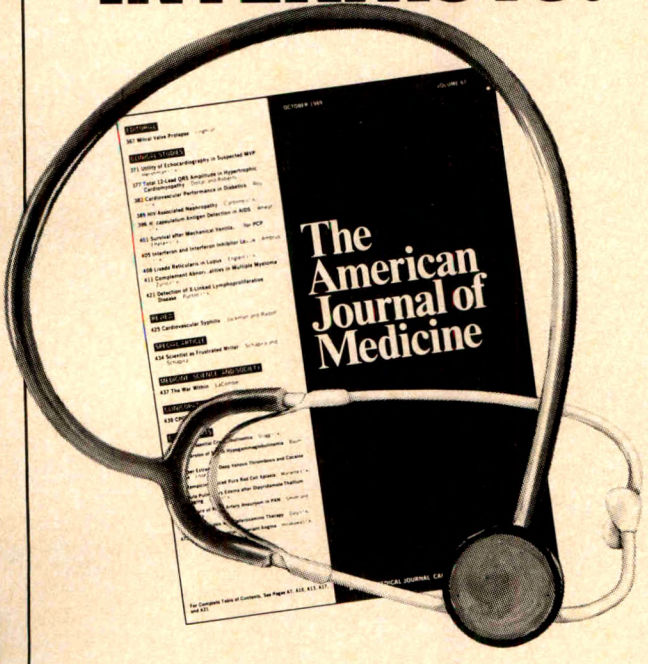
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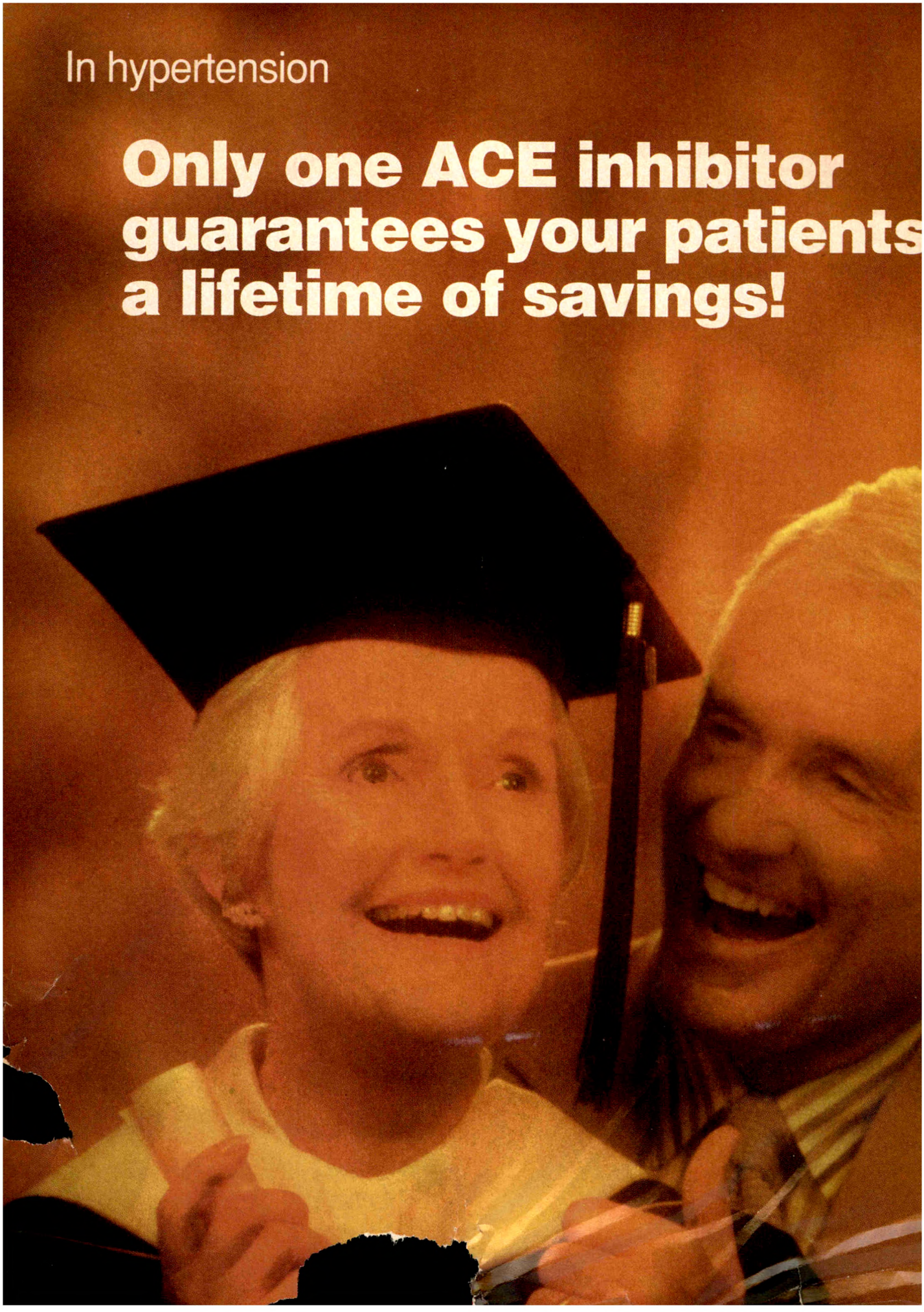
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Angioedema has been reported in patients receiving ACE inhibitors. Because ACE inhibitors can cause injury and even death to the developing fetus, when pregnancy is detected ACE inhibitors should be discontinued as soon as possible. Please consult brief summary of Prescribing Information on last pages.

CIBA

Lotensin®
benazepril hydrochloride
Tablets

BRIEF SUMMARY. FOR FULL PRESCRIBING INFORMATION, SEE PACKAGE INSERT

Use in Pregnancy
When used in pregnancy during the second and third trimesters, ACE inhibitors can cause injury and even death to the developing fetus. When pregnancy is detected, Lotensin should be discontinued as soon as possible. See WARNINGS, Fetal/Neonatal Morbidity and Mortality.

INDICATIONS AND USAGE
Lotensin is indicated for the treatment of hypertension. It may be used alone or in combination with thiazide diuretics.

In using Lotensin, consideration should be given to the fact that another angiotensin-converting enzyme inhibitor, captopril, has caused agranulocytosis, particularly in patients with renal impairment or collagen-vascular disease. Available data are insufficient to show that Lotensin does not have a similar risk (see WARNINGS).

CONTRAINDICATIONS
Lotensin is contraindicated in patients who are hypersensitive to this product or to any other ACE inhibitor.

WARNINGS
Angioedema
Angioedema of the face, extremities, lips, tongue, glottis, and larynx has been reported in patients treated with angiotensin-converting enzyme inhibitors. In U.S. clinical trials, symptoms consistent with angioedema were seen in none of the subjects who received placebo and in about 0.5% of the subjects who received Lotensin. Angioedema associated with laryngeal edema can be fatal. If laryngeal stridor or angioedema of the face, tongue, or glottis occurs, treatment with Lotensin should be discontinued and appropriate therapy instituted immediately. **Where there is involvement of the tongue, glottis, or larynx, likely to cause airway obstruction, appropriate therapy, e.g., subcutaneous epinephrine injection 1:1000 (0.3 mL to 0.5 mL) should be promptly administered (see ADVERSE REACTIONS).**

Hypotension
Lotensin can cause symptomatic hypotension. Like other ACE inhibitors, benazepril has been only rarely associated with hypotension in uncomplicated hypertensive patients. Symptomatic hypotension is most likely to occur in patients who have been volume- and/or salt-depleted as a result of prolonged diuretic therapy, dietary salt restriction, dialysis, diarrhea, or vomiting. Volume- and/or salt-depletion should be corrected before initiating therapy with Lotensin.

In patients with congestive heart failure, with or without associated renal insufficiency, ACE inhibitor therapy may cause excessive hypotension, which may be associated with oliguria or azotemia and, rarely, with acute renal failure and death. In such patients, Lotensin therapy should be started under close medical supervision; they should be followed closely for the first 2 weeks of treatment and whenever the dose of benazepril or diuretic is increased.

If hypotension occurs, the patient should be placed in a supine position, and, if necessary, treated with intravenous infusion of physiological saline. Lotensin treatment usually can be continued following restoration of blood pressure and volume.

Neutropenia/Agranulocytosis
Another angiotensin-converting enzyme inhibitor, captopril, has been shown to cause agranulocytosis and bone marrow depression, rarely in uncomplicated patients, but more frequently in patients with renal impairment, especially if they also have a collagen-vascular disease such as systemic lupus erythematosus or scleroderma. Available data from clinical trials of benazepril are insufficient to show that benazepril does not cause agranulocytosis at similar rates. Monitoring of white blood cell counts should be considered in patients with collagen-vascular disease, especially if the disease is associated with impaired renal function.

Fetal/Neonatal Morbidity and Mortality
ACE inhibitors can cause fetal and neonatal morbidity and death when administered to pregnant women. Several dozen cases have been reported in the world literature. When pregnancy is detected, ACE inhibitors should be discontinued as soon as possible.

The use of ACE inhibitors during the second and third trimesters of pregnancy has been associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death. Oligohydramnios has also been reported, presumably resulting from decreased fetal renal function; oligohydramnios in this setting has been associated with fetal limb contractures, craniofacial deformation, and hypoplastic lung development. Prematurity, intrauterine growth retardation, and patent ductus arteriosus have also been reported, although it is not clear whether these occurrences were due to the ACE inhibitor exposure.

These adverse effects do not appear to have resulted from intrauterine ACE inhibitor exposure that has been limited to the first trimester. Mothers whose embryos and fetuses are exposed to ACE inhibitors only during the first trimester should be so informed. Nonetheless, when patients become pregnant, physicians should make every effort to discontinue the use of benazepril as soon as possible.

Rarely (probably less often than once in every thousand pregnancies), no alternative to ACE inhibitors will be found. In these rare cases, the mothers should be apprised of the potential hazards to their fetuses, and serial ultrasound examinations should be performed to assess the intraamniotic environment.

If oligohydramnios is observed, benazepril should be discontinued unless it is considered life-saving for the mother. Contraction stress testing (CST), a nonstress test (NST), or biophysical profiling (BPP) may be appropriate, depending upon the week of pregnancy. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury.

Infants with histories of *in utero* exposure to ACE inhibitors should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion. Exchange transfusion or dialysis may be required as means of reversing hypotension and/or substituting for disordered renal function. Benazepril, which crosses the placenta, can theoretically be removed from the neonatal circulation by these means; there are occasional reports of benefit from these maneuvers with another ACE inhibitor, but experience is limited.

No teratogenic effects of Lotensin were seen in studies of pregnant rats, mice, and rabbits. On a mg/m^2 basis, the doses used in these studies were 60 times (in rats), 9 times (in mice), and more than 0.8 times (in rabbits) the maximum recommended human dose (assuming a 50 kg woman). On a mg/kg basis these multiples are 300 times (in rats), 90 times (in mice) and more than 3 times (in rabbits) the maximum recommended human dose.

PRECAUTIONS
General
Impaired Renal Function: As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients with severe congestive heart failure whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with angiotensin-converting enzyme inhibitors, including Lotensin, may be associated with oliguria and/or progressive azotemia and (rarely) with acute renal failure and/or death. In a small study of hypertensive patients with renal artery stenosis in a solitary kidney or bilateral renal artery stenosis, treatment with Lotensin was associated with increases in blood urea nitrogen and serum creatinine; these increases were reversible upon discontinuation of Lotensin or diuretic therapy, or both. When such patients are treated with ACE inhibitors, renal function should be monitored during the first few weeks of therapy. Some hypertensive patients with no apparent preexisting renal vascular disease have developed increases in blood urea nitrogen and serum creatinine, usually minor and transient, especially when Lotensin has been given concomitantly with a diuretic. This is more likely to occur in patients with preexisting renal impairment. Dosage reduction of Lotensin and/or discontinuation of the diuretic may be required. **Evaluation of the hypertensive patient should always include assessment of renal function (see DOSAGE AND ADMINISTRATION).**

Hyperkalemia: In clinical trials, hyperkalemia (serum potassium at least 0.5 mEq/L greater than the upper limit of normal) occurred in approximately 1% of hypertensive patients receiving Lotensin. In most cases, these were isolated values which resolved despite continued therapy. Risk factors for the development of hyperkalemia include renal insufficiency, diabetes mellitus, and the concomitant use of potassium-sparing diuretics, potassium supplements, and/or potassium-containing salt substitutes, which should be used cautiously, if at all, with Lotensin (see Drug Interactions).

Cough: Cough has been reported with the use of ACE inhibitors. Characteristically, the cough is nonproductive, persistent, and resolves after discontinuation of therapy. ACE inhibitor-induced cough should be considered as part of the differential diagnosis of cough.

Impaired Liver Function: In patients with hepatic dysfunction due to cirrhosis, levels of benazeprilat are essentially unaltered.

Surgery/Anesthesia: In patients undergoing surgery or during anesthesia with agents that produce hypotension, benazepril will block the angiotensin II formation that could otherwise occur secondary to compensatory renin release. Hypotension that occurs as a result of this mechanism can be corrected by volume expansion.

Information for Patients
Pregnancy: Female patients of childbearing age should be told about the consequences of second- and third-trimester exposure to ACE inhibitors, and they should also be told that these consequences do not appear to have resulted from intrauterine ACE inhibitor exposure that has been limited to the first trimester. These patients should be asked to report pregnancies to their physicians as soon as possible.

Angioedema: Angioedema, including laryngeal edema, can occur with treatment with ACE inhibitors, especially following the first dose. Patients should be so advised and told to report immediately any signs or symptoms suggesting angioedema (swelling of face, eyes, lips, or tongue, or difficulty in breathing) and to take no more drug until they have consulted with the prescribing physician.

Symptomatic Hypotension: Patients should be cautioned that lightheadedness can occur, especially during the first days of therapy, and it should be reported to the prescribing physician. Patients should be told that if syncope occurs, Lotensin should be discontinued until the prescribing physician has been consulted.

All patients should be cautioned that inadequate fluid intake or excessive perspiration, diarrhea, or vomiting can lead to an excessive fall in blood pressure, with the same consequences of lightheadedness and possible syncope.

Hyperkalemia: Patients should be told not to use potassium supplements or salt substitutes containing potassium without consulting the prescribing physician.

Neutropenia: Patients should be told to promptly report any indication of infection (e.g., sore throat, fever), which could be a sign of neutropenia.

Drug Interactions
Diuretics: Patients on diuretics, especially those in whom diuretic therapy was recently instituted, may occasionally experience an excessive reduction of blood pressure after initiation of therapy with Lotensin. The possibility of hypotensive effects with Lotensin can be minimized by either discontinuing the diuretic or increasing the salt intake prior to initiation of treatment with Lotensin. If this is not possible, the starting dose should be reduced (see DOSAGE AND ADMINISTRATION).

Potassium Supplements and Potassium-Sparing Diuretics: Lotensin can attenuate potassium loss caused by thiazide diuretics. Potassium-sparing diuretics (spironolactone, amiloride, triamterene, and others) or potassium supplements can increase the risk of hyperkalemia. Therefore, if concomitant use of such agents is indicated, they should be given with caution, and the patient's serum potassium should be monitored frequently.

Oral Anticoagulants: Interaction studies with warfarin and acenocoumarol failed to identify any clinically important effects on the serum concentrations or clinical effects of these anticoagulants.

Lithium: Increased serum lithium levels and symptoms of lithium toxicity have been reported in patients receiving ACE inhibitors during therapy with lithium. These drugs should be coadministered with caution, and frequent monitoring of serum lithium levels is recommended. If a diuretic is also used, the risk of lithium toxicity may be increased.

Other: No clinically important pharmacokinetic interactions occurred when Lotensin was administered concomitantly with hydrochlorothiazide, chlorthalidone, furosemide, digoxin, propranolol, atenolol, naproxen, or cimetidine.

Lotensin has been used concomitantly with beta-adrenergic-blocking agents, calcium-channel-blocking agents, diuretics, digoxin, and hydralazine, without evidence of clinically important adverse interactions. Benazepril, like other ACE inhibitors, has had less than additive effects with beta-adrenergic blockers, presumably because both drugs lower blood pressure by inhibiting parts of the renin-angiotensin system.

Carcinogenesis, Mutagenesis, Impairment of Fertility
No evidence of carcinogenicity was found when benazepril was administered to rats and mice for up to two years at doses of up to 150 mg/kg/day. When compared on the basis of body weights, this dose is 110 times the maximum recommended human dose. When compared on the basis of body surface areas, this dose is 18 and 9 times (rats and mice, respectively) the maximum recommended human dose (calculations assume a patient weight of 60 kg). No mutagenic activity was detected in the Ames test in bacteria (with or without metabolic activation), in an in vitro test for forward mutations in cultured mammalian cells, or in a nucleus anomaly test. In doses of 50-500 mg/kg/day (6-60 times the maximum recommended human dose based on mg/m^2 comparison and 37-375 times the maximum recommended human dose based on a mg/kg comparison), Lotensin had no adverse effect on the reproductive performance of male and female rats.

Pregnancy Categories C (first trimester) and D (second and third trimesters)
See WARNINGS, Fetal/Neonatal Morbidity and Mortality.

Nursing Mothers
Minimal amounts of unchanged benazepril and of benazeprilat are excreted into the breast milk of lactating women treated with benazepril. A newborn child ingesting entirely breast milk would receive less than 0.1% of the mg/kg maternal dose of benazepril and benazeprilat.

Geriatric Use
Of the total number of patients who received benazepril in U.S. clinical studies of Lotensin, 18% were 65 or older while 2% were 75 or older. No overall differences in effectiveness or safety were observed between these patients and younger patients, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Pediatric Use
Safety and effectiveness in children have not been established.

ADVERSE REACTIONS
Lotensin has been evaluated for safety in over 6000 patients with hypertension; over 700 of these patients were treated for at least one year. The overall incidence of reported adverse events was comparable in Lotensin and placebo patients.

The reported side effects were generally mild and transient, and there was no relation between side effects and age, duration of therapy, or total dosage within the range of 2 to 80 mg. Discontinuation of therapy because of a side effect was required in approximately 5% of U.S. patients treated with Lotensin and in 3% of patients treated with placebo.

The most common reasons for discontinuation were headache (0.6%) and cough (0.5%). (See PRECAUTIONS, Cough).

The side effects considered possibly or probably related to study drug that occurred in U.S. placebo-controlled trials in more than 1% of patients treated with Lotensin are shown below.

PATIENTS IN U.S. PLACEBO-CONTROLLED STUDIES

	LOTENSIN (N = 964)		PLACEBO (N = 496)	
	N	%	N	%
Headache	60	6.2	21	4.2
Dizziness	35	3.6	12	2.4
Fatigue	23	2.4	11	2.2
Somnolence	15	1.6	2	0.4
Postural Dizziness	14	1.5	1	0.2
Nausea	13	1.3	5	1.0
Cough	12	1.2	5	1.0

Other adverse experiences reported in controlled clinical trials (in less than 1% of benazepril patients), and rarer events seen in postmarketing experience, include the following (in some, a causal relationship to drug use is uncertain):

Cardiovascular: Symptomatic hypotension was seen in 0.3% of patients, postural hypotension in 0.4%, and syncope in 0.1%; these reactions led to discontinuation of therapy in 4 patients who had received benazepril monotherapy and in 9 patients who had received benazepril with hydrochlorothiazide (see PRECAUTIONS and WARNINGS). Other reports included angina pectoris, palpitations, and peripheral edema.

Renal: Of hypertensive patients with no apparent preexisting renal disease, about 2% have sustained increases in serum creatinine to at least 150% of their baseline values while receiving Lotensin, but most of these increases have disappeared despite continuing treatment. A much smaller fraction of these patients (less than 0.1%) developed simultaneous (usually transient) increases in blood urea nitrogen and serum creatinine.

Fetal/Neonatal Morbidity and Mortality: See WARNINGS, Fetal/Neonatal Morbidity and Mortality.

Angioedema: Angioedema has been reported in patients receiving ACE inhibitors. During clinical trials in hypertensive patients with benazepril, 0.5% of patients experienced edema of the lips or face without other manifestations of angioedema. Angioedema associated with laryngeal edema and/or shock may be fatal. If angioedema of the face, extremities, lips, tongue, or glottis and/or larynx occurs, treatment with Lotensin should be discontinued and appropriate therapy instituted immediately (see WARNINGS).

Gastrointestinal: Constipation, gastritis, vomiting, and melena.

Dermatologic: Apparent hypersensitivity reactions (manifested by dermatitis, pruritus, or rash) and flushing.

Neurologic and Psychiatric: Anxiety, decreased libido, hypertonia, insomnia, nervousness, and paresthesia.

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Other: Arthralgia, arthritis, asthenia, asthma, bronchitis, dyspnea, impotence, infection, myalgia, sinusitis, sweating, and urinary tract infection.

Clinical Laboratory Test Findings

Creatinine and Blood Urea Nitrogen: Of hypertensive patients with no apparent preexisting renal disease, about 2% have sustained increases in serum creatinine to at least 150% of their baseline values while receiving Lotensin, but most of these increases have disappeared despite continuing treatment. A much smaller fraction of these patients (less than 0.1%) developed simultaneous (usually transient) increases in blood urea nitrogen and serum creatinine. None of these increases required discontinuation of treatment. Increases in these laboratory values are more likely to occur in patients with renal insufficiency or those pretreated with a diuretic and, based on experience with other ACE inhibitors, would be expected to be especially likely in patients with renal artery stenosis (see PRECAUTIONS, General).

Potassium: Since benazepril decreases aldosterone secretion, elevation of serum potassium can occur. Potassium supplements and potassium-sparing diuretics should be given with caution, and the patient's serum potassium should be monitored frequently (see PRECAUTIONS).

Hemoglobin: Decreases in hemoglobin (a low value and a decrease of 5 g/dL) were rare, occurring in only 1 of 2014 patients receiving Lotensin alone and in 1 of 1357 patients receiving Lotensin plus a diuretic. No U.S. patients discontinued treatment because of decreases in hemoglobin.

Other (causal relationships unknown): Clinically important changes in standard laboratory tests were rarely associated with Lotensin administration. Elevations of liver enzymes, serum bilirubin, uric acid, and blood glucose have been reported, as have scattered incidents of hyponatremia, electrocardiographic changes, leukopenia, eosinophilia, and proteinuria. In U.S. trials, less than 0.5% of patients discontinued treatment because of laboratory abnormalities.

OVERDOSAGE

Single oral doses of 3 g/kg benazepril were associated with significant lethality in mice. Rats however, tolerated single oral doses of up to 6 g/kg. Reduced activity was seen at 1 g/kg in mice and at 5 g/kg in rats. Human overdoses of benazepril have not been reported, but the most common manifestation of human benazepril overdosage is likely to be hypotension.

Laboratory determinations of serum levels of benazepril and its metabolites are not widely available, and such determinations have, in any event, no established role in the management of benazepril overdose.

No data are available to suggest physiological maneuvers (e.g., maneuvers to change the pH of the urine) that might accelerate elimination of benazepril and its metabolites. Benazeprilat can be removed from the body by dialysis, but this intervention should rarely, if ever, be required.

Angiotensin II could presumably serve as a specific antagonist-antidote in the setting of benazepril overdose, but angiotensin II is essentially unavailable outside of scattered research facilities. Because the hypotensive effect of benazepril is achieved through vasodilation and effective hypovolemia, it is reasonable to treat benazepril overdose by infusion of normal saline solution.

Storage: Do not store above 86° F (30° C). Protect from moisture.

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Left Ventricular Function After Reversal of Myocardial Hypertrophy in Systemic Hypertension, and Response to Acute Increase of Afterload by Cold Pressor Test

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Using digitized M-mode echocardiography, the left ventricular (LV) response to acute increase in blood pressure after regression of myocardial hypertrophy due to an effective antihypertensive treatment was evaluated. Fifteen hypertensive patients with basal LV hypertrophy (LV mass >230 g, and normal LV diastolic diameter) and normal LV mass after 3 to 4 months of treatment with angiotensin-converting enzyme inhibitors were selected for study. Subjects performed a cold pressor test before and after therapy. LV systolic function was normal in all subjects. LV diastolic function (impaired at basal evaluation in 13 subjects) improved after therapy in all subjects, with normalization in 10. Before treatment, the cold pressor test induced significant increases in blood pressure and heart rate without changes in LV parameters. After regression of hypertrophy, the cold pressor test induced increases in hemodynamic parameters comparable to those of the basal test, and LV parameters remained unchanged. Our results indicate that regression of myocardial hypertrophy induced by angiotensin-converting enzyme inhibitors does not impair the ability of the left ventricle to face acute increases in afterload. The improvement in LV diastolic function (found at rest after reversal of hypertrophy) persists during the cold pressor test, which confirms that it is primarily due to LV mass reduction and is not simply a consequence of decrease in afterload induced by treatment.

(Am J Cardiol 1992;69:1439–1441)

Many studies demonstrated that different kinds of antihypertensive drugs can induce regression of left ventricular (LV) hypertrophy.[1–8] Because LV hypertrophy is an important adaptive mechanism that normalizes wall stress and influences LV performance,[9,10] it is necessary to establish the effects of regression of hypertrophy on LV systolic and diastolic function. However, assessment of these effects is difficult because of a number of variables that could contribute to changes in LV function. The principal variable (in addition to regression of hypertrophy itself) is the decrease in afterload. Many studies evaluated LV performance after regression of hypertrophy only at rest, with blood pressure reduced by treatment, whereas few and controversial data are available concerning the effect of LV mass reduction on LV performance during acute increases in afterload.[11–14]

Therefore, we evaluated the LV response to acute increase in afterload induced by cold pressor stress before and after regression of LV hypertrophy due to an effective antihypertensive treatment. We selected subjects treated with the same kind of drugs (angiotensin-converting enzyme inhibitors), because not only blood pressure reduction and changes in LV mass, but also the antihypertensive drug used can influence LV function.

METHODS

Study group: We selected 33 hypertensive patients with LV hypertrophy (LV mass >230 g, and normal LV diameter) at the basal evaluation assigned to treatment with angiotensin-converting enzyme inhibitors. Other selection criteria were as follows: (1) M-mode LV echogram of good quality and reproducibility; (2) absence of clinical, radiologic, electrocardiographic or echocardiographic evidence of heart failure, myocardial infarction, angina pectoris, or congenital or valvular heart disease; (3) no previous antihypertensive treatment, or withdrawal of therapy for ≥1 month at the basal evaluation; and (4) absence of systemic diseases, such as diabetes mellitus, or disorders of the connective tissue, which could induce changes in LV structure and function.

Patients were judged to have essential hypertension on the basis of history, physical examination and laboratory findings. Subjects performed a cold pressor test by immersion of a hand up to the wrist in iced water for 2 minutes. Arterial blood pressure and LV M-mode

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TABLE I Mean Values of Hemodynamic and Left Ventricular Parameters at Rest and During Cold Pressor Test

	Basal		Therapy	
	Rest	Cold Stress	Rest	Cold Stress
Systolic pressure (mm Hg)	182 ± 15	208 ± 17*	146 ± 11†	171 ± 12*
Diastolic pressure (mm Hg)	111 ± 7	132 ± 9*	81 ± 6†	104 ± 7*
Heart rate (beats/min)	75 ± 12	82 ± 9‡	74 ± 8	83 ± 10‡
LV diastolic diameter (mm)	48 ± 4	47 ± 3	48 ± 4	46 ± 5
$-dD/dt$ (s^{-1})	3.62 ± 0.92	3.66 ± 0.94	3.68 ± 0.87	3.69 ± 0.85
$+dD/dt$ (s^{-1})	3.41 ± 0.61	3.70 ± 0.58	4.32 ± 0.54§	4.38 ± 0.49
End-systolic stress (dyne/cm^2)	53 ± 9	74 ± 11*	48 ± 8	70 ± 9*
Systemic resistances (dynes s cm^{-5})	1,732 ± 198	1,985 ± 164*	1,273 ± 185†	1,467 ± 172*

*$p < 0.001$, ‡$p < 0.01$, rest versus cold stress.
†$p < 0.001$, §$p < 0.005$, basal versus therapy.
$-dD/dt$ = peak shortening rate of LV diameter; $+dD/dt$ = peak lengthening rate of LV diameter; LV = left ventricular.

echogram were recorded immediately before and after immersion. The cold pressor test was repeated by 15 patients (9 men and 6 women, age range 33 to 56 years) who had normal LV mass after 3 to 4 months of successful antihypertensive treatment (10 treated with perindopril [4 to 8 mg once daily], and 5 with captopril [25 to 50 mg twice daily]). The study was approved by the ethical committee of the University of Pavia's Department of Internal Medicine, and all patients gave informed consent.

Echocardiographic methods: All LV M-mode echocardiograms were recorded (paper speed 50 mm/s) under 2-dimensional control with an HP Sonos 1000. A simultaneous electrocardiogram was obtained in all subjects. Echocardiograms were digitized, as originally described by Gibson and Brown,[15] using an HP 9111 graphic tablet and subsequently processed by an HP 1000 minicomputer. All echocardiograms were blindly evaluated by 1 operator who digitized 4 consecutive cardiac cycles of each echogram. The minicomputer processed digitized data, averaging the 4 cardiac cycles, and the following measurements were obtained from the computer output: (1) LV end-diastolic and end-systolic diameters; (2) end-diastolic thickness of ventricular septum; (3) end-diastolic and end-systolic thicknesses of posterior wall; (4) LV mass[16]; (5) peak shortening rate of LV diameter in systole ($-dD/dt$); (6) peak lengthening rate of LV diameter in diastole ($+dD/dt$); (7) total systemic vascular resistances[17] calculated using the echocardiographically derived cardiac output; and (8) end-systolic wall stress.[18]

These parameters were compared with the normal values of our echocardiographic laboratory obtained from the examination of 200 normal adults.

The reproducibility of echocardiographic measurements was tested on 20 normal subjects (each examined 3 times) with the same ultrasonic technique; the same operator digitized 4 consecutive cardiac cycles of each echogram. The coefficients of variation were as follows: LV end-diastolic diameter 0.4%; septal thickness 3.2%; posterior wall thickness 3.4%; peak shortening rate 1.1%; and peak lengthening rate 5.3%.

Statistical analysis: Statistical evaluation of the results was performed using paired and unpaired Student's t tests, and linear regression analysis. A p value <0.05 was considered statistically significant.

RESULTS

After treatment, systolic and diastolic blood pressures were significantly decreased (Table I). The reduction in blood pressure was associated with a significant decrease in systemic vascular resistances, without changes in heart rate and cardiac output (5.3 ± 1.8 to 5.5 ± 2.1 liters/min) (Table I).

As a consequence of the selection criteria, at the basal evaluation all subjects had increased LV mass due to increased wall and septal thickness (septal/wall thickness <1.3), with normal LV diastolic diameter (<56 mm). After treatment all patients had normalization of LV mass (302 ± 23 to 193 ± 21 g; $p < 0.001$), with no changes in LV diameter. Before therapy, LV diastolic function was impaired ($+dD/dt < 3.6\ s^{-1}$) in 13 subjects, and systolic function was normal in all ($-dD/dt > 1.9\ s^{-1}$). After regression of myocardial hypertrophy, the average $+dD/dt$ increased significantly (Table I). $+dD/dt$ increased in the 13 patients with basal diastolic impairment, with normalization in 10. Average and individual values of $-dD/dt$ remained unchanged after treatment. End-systolic stress did not change significantly after therapy (Table I).

The cold pressor test before treatment induced significant increases in systolic and diastolic blood pressures, systemic vascular resistances, heart rate and end-systolic stress; LV diameters, and $-dD/dt$ and $+dD/dt$ did not change significantly. After regression of myocardial hypertrophy, the cold pressor test induced increases in hemodynamic parameters comparable to those at basal evaluation; LV parameters remained unchanged (Table I). At the basal evaluation, we found at rest and during the cold pressor test significant inverse correlations between end-systolic stress and $-dD/dt$ ($r = -0.81$, cold pressor test $r = -0.78$; $p < 0.005$), and $+dD/dt$ ($r = -0.63$, cold pressor test $r = -0.60$; $p < 0.01$), and between LV mass and $+dD/dt$ ($r = -0.68$, cold pressor test $r = -0.61$; $p < 0.01$). After regression of hypertrophy, the correlation between end-systolic stress and $-dD/dt$ did not change ($r = -0.83$, cold pressor test $r = -0.81$; $p < 0.005$), whereas that between

LV mass and +dD/dt disappeared ($r = -0.23$, cold pressor test $r = -0.18$), and that between end-systolic stress and +dD/dt increased ($r = -0.80$, cold pressor test $r = -0.84$; $p < 0.005$).

DISCUSSION

In accordance with previous clinical studies,[2,3,7,8,19] our results confirm the efficacy of angiotensin-converting enzyme inhibitors as antihypertensive agents and demonstrate that these kinds of drugs can reverse hypertension-related LV hypertrophy. The reduction of LV mass was accompanied in our patients by a significant improvement in LV relaxation, without impairment of LV systolic performance at rest. Because changes in blood pressure interfere with LV function, we studied the correlation between end-systolic stress and parameters of LV function before and after treatment to avoid the effects of reduced afterload on LV performance. After regression of hypertrophy, we found at rest no changes in the pretreatment inverse correlation between afterload and −dD/dt, and disappearence of the basal correlation between LV mass and the index of diastolic function (which became more closely related with afterload). The results suggest that improvement in LV relaxation was due primarily to regression of hypertrophy that did not induce any reduction in LV systolic function. Many studies found at rest (with blood pressure well controlled by treatment) no changes in systolic function, and a significant improvement in LV diastolic performance after regression of LV hypertrophy.[2,7,8,20–22]

Many doubts still persist concerning the consequences of LV mass reduction on the ability of the left ventricle to face acute increases in afterload due to inappropriate withdrawal of therapy or to physical or mental stress. Experimental studies in rats showed controversial results; after reversal of hypertrophy, some investigators found, during an acute increase in afterload, a significant impairment of cardiac performance,[11,14] whereas others found no deterioration or an improvement in ventricular systolic function.[12,13] To obtain information concerning this problem, we studied the LV response to acute increase in afterload induced by cold pressor test before and after regression of LV hypertrophy.

At the basal evaluation, the acute increase in afterload induced by the cold pressor test through α-receptor stimulation was accompanied in our patients by no changes in LV systolic and diastolic function. After therapy, the cold stress determined an increase in blood pressure and end-systolic stress comparable to that at the basal test, and the LV functional parameters remained unchanged. Furthermore, the correlations between end-systolic stress and LV systolic and diastolic parameters did not change during stress.

These results indicate that regression of myocardial hypertrophy induced by angiotensin-converting enzyme inhibitors does not impair the ability of the left ventricle to face acute increases in afterload. Furthermore, it should be noted that the improvement in diastolic function found at rest after regression of hypertrophy persists also during the blood pressure increase by cold stress, which confirms that it is primarily due to LV mass reduction and is not simply a consequence of decrease in afterload induced by treatment.

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Preoperative Diagnosis of Coronary Artery Disease in Patients with Valvular Heart Disease Using Technetium-99m Isonitrile Tomographic Imaging Together with High-Dose Dipyridamole and Handgrip Exercise

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Forty-seven consecutive patients (mean age 61 ± 8 years) referred for cardiac catheterization due to moderate to severe aortic (n = 30) or mitral (n = 17) valvular heart disease were examined by technetium-99m isonitrile tomography together with a high-dose dipyridamole infusion (0.7 mg/kg) and handgrip stress. Tomography did not identify coronary artery disease (CAD) in 3 of the 21 patients with angiographically proven disease (sensitivity 86%) and suggested false positive results in 5 of the 26 without the disease (specificity 81% and negative predictive accuracy 88%). No patient without angina pectoris and with negative scintigraphy (n = 14) had angiographically significant (≥50% diameter stenosis) CAD. Overall vessel sensitivity was 63%, and specificity was 92%. The frequency of side effects during the dipyridamole-handgrip test was only 7%. No serious complications occurred during stress tests.

Thus, technetium-99m isonitrile tomographic imaging, together with high-dose dipyridamole and handgrip exercise, is a useful noninvasive method in excluding significant CAD in patients with valvular heart disease.

(Am J Cardiol 1992;69:1442–1445)

The exclusion of significant coronary artery disease (CAD) is often a prerequisite for avoiding cardiac catheterization before valvular heart surgery. In previous studies with thallium scintigraphy, sensitivities of up to 90% were attained in the detection of CAD among patients with valvular heart disease.[1–3]

Old age, and disease-linked incapacity and risks limit the use of dynamic exercise tests in patients with valvular heart disease,[4] and therefore, dipyridamole infusion in the context of nuclear studies performed in these patients appears plausible. The usefulness of dipyridamole infusion as a substitute for dynamic exercise was previously validated by us[3] and other investigators,[5] and although recently criticized,[6] was suggested to be especially suitable for patients undergoing preoperative evaluation for noncardiac surgery,[7,8] as well as for asymptomatic patients.[9]

In an animal experimental study, dipyridamole was suggested to be especially well-suited for imaging with technetium-99m isonitrile (MIBI)[10]; this was also recently proposed by us in patients with known CAD.[11] The present study was designed to test the ability of MIBI to detect CAD in patients with valvular heart disease needing replacement surgery. A high-dose, intravenous dipyridamole treatment together with handgrip isometric exercise was used as a stress method.[2]

METHODS

Patients: Forty-seven consecutive patients (20 women and 27 men, mean age 61 ± 8 years) admitted to our hospital for aortic or mitral valvular heart surgery were referred preoperatively to both coronary angiography and MIBI tomography after giving informed consent. The protocol was approved by the ethics committee of the hospital. All patients were examined by 2-dimensional, M-mode and Doppler echocardiography, and the existence of left ventricular hypertrophy was stated if the ventricular septal thickness was ≥15 mm. Patients with combined lesions of 1 valve were classified according to the most severe component of the lesion. Patients with both aortic and mitral valvular diseases (n = 2) were classified according to the most severely affected valve. Severity of the valvular lesions was determined as follows: moderate/severe aortic stenosis: mean systolic transvalvular pressure gradient ≤/>50 mmHg[12]; moderate/severe mitral stenosis: valve areas ≥/<1 cm^2; and moderate or severe aortic or mitral regurgitation: cine-

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angiographic regurgitation index 3+/4 or 4+/4, using a standard visual scale.[13]

Coronary angiography: Selective biplane coronary angiography in multiple projections including cranial and caudal views was performed by the Judkins technique. Stenoses of coronary arteries were quantified by the digitized draw-analysis of stenotic segments on end-diastolic cineframes in 2 projections.[11] A coronary luminal diameter reduction of ≥50% was considered to be a significant lesion.

Dipyridamole handgrip test: Dipyridamole was infused through a peripheral venous cannula at a rate of 0.175 mg/kg/min for 4 minutes, with a total dose of 0.7 mg/kg.[11] One and a half minutes after the end of dipyridamole infusion, patients performed a handgrip exercise in a sitting position by squeezing a hand dynamometer at a force of 50% of the mean maximal voluntary contraction for 1.5 minutes. The intravenous isotope injection was administered 1 minute before ending the squeezing. If severe symptoms developed or if blood pressure decreased >20 mm Hg, aminophylline (50 to 100 mg) was administered, and in cases of anginal chest pain, sublingual nitroglycerin was given.

Technetium-99m isonitrile tomography: The isotope study was performed according to the 1-day stress-rest principle, either before or after coronary angiography within the time domain of 1 month. Long-acting nitrates were discontinued on the day of examination. The doses of MIBI (Cardiolite®) were approximately 8 mCi (300 MBq) for the exercise study, and approximately 20 mCi (740 MBq) for the resting study 3 to 4 hours later.

Imaging data was acquired as 64 × 64 matrix using the Siemens Rota™ ZLC/75 gamma camera equipped with a low-energy, all-purpose collimator over 180°, beginning from the 45° left posterior oblique projection and collecting 30 images every 6° for 35 seconds each, with a total acquisition time of 20 minutes.[11] An exercise/rest profile ratio was also calculated, and a bullseye analysis was performed in controversial cases.

Scintigraphs (Figure 1) were interpreted independently by 2 observers who were not aware of the angiographic findings. Five discrete regions of the left ventricular myocardium (anterior, septal, inferior, posterolateral and apical) were defined. The vascular territories were described as follows: the anterior or septal (or both), or apical segment to the left anterior descending artery, the inferior segment to the right coronary artery, and the posterolateral segment to the left circumflex coronary artery. Regional perfusion was considered abnormal if a defect was visually present in ≥2 tomographic slices (thickness of 12 mm each) with or without redistribution. Complete agreement between the observers concerning the presence or absence of ischemia was achieved in 41 of 47 cases (87%). Disagreement concerning the results was resolved by discussion. Intraindividual variation in interpretation of the images was 5%.

Statistics: Results were expressed as mean ± SD. The significance of differences between the mean values was tested by Student's *t* test.

RESULTS

Clinical and angiographic data: The study cohort comprised 30 patients with aortic valvular disease (22 with aortic stenosis), and 17 with mitral valvular disease (13 with mitral stenosis). Most patients (n = 33) were in New York Heart Association functional class III, with only 3 in class IV. Cardiac catheterization revealed severe valve disease in 23 of the 47 patients. Coronary arteriography revealed significant CAD in 21 patients (9 with 1-vessel and 12 with multivessel disease). Among these patients, CAD was suspected on the basis of clinical data (previous myocardial infarction [n = 3] or angina pectoris, or both) in 15, but it was also suggested in 10 with a normal finding by coronary angiography.

Tomographic data: MIBI tomography did not prove angiographically evident disease in 3 cases (sensitivity 86%) (Figure 2). All 3 patients presenting false negative scans had angina pectoris, and 2 of them had multivessel disease by angiography. Five patients with normal coronary arteriograms showed false positive isotope scans (specificity 81%).

Of 38 angiographically diseased vessels, MIBI tomography correctly identified 24 (13 of 21 vessels with >70% luminal diameter stenosis). Only 2 of the 14 diseased vessels with false negative scans demonstrated a collateral connection in angiography. Vessel sensitivities were as follows: 63% for left anterior descending artery, 29% for left circumflex, and 83% for right coronary. When the territories of the left circumflex and right coronary arteries were assessed together, a "2-vessel" sensitivity of 79% was achieved. Overall vessel sensitivity was 63% (62% for vessels with >70% luminal diameter stenosis). Of 103 vessel distributions with normal or nonsignificant findings by angiography, isotope tomog-

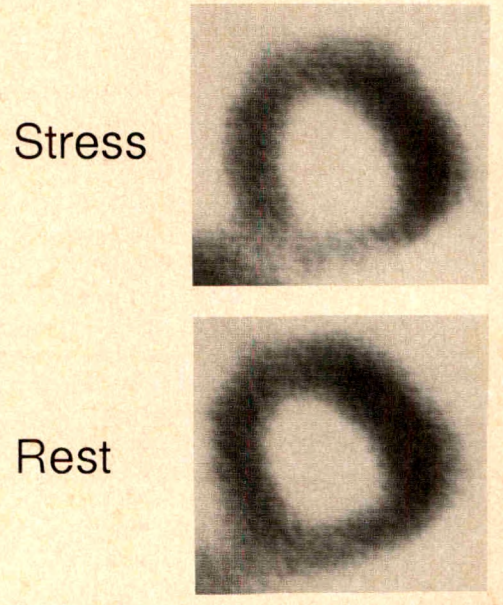


FIGURE 1. Technetium-99m isonitrile tomography study of 64-year-old man with mitral stenosis and secondary pulmonary hypertension. An 88% stenosis in dominant distal right coronary artery was revealed by coronary angiography. Reversible inferior defect is seen in stress image. Stress = dipyridamole infusion and handgrip exercise.

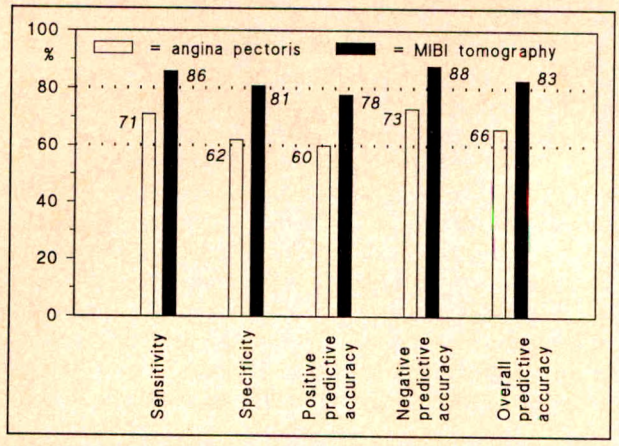


FIGURE 2. Indexes of test performance of angina pectoris and technetium-99m isonitrile (MIBI) tomography in detection of coronary artery disease in 47 patients with valvular heart disease.

raphy suggested 8 false positive findings (overall vessel specificity 92%) in 8 patients (2 women). All but 1 false positive test result was associated with aortic valve disease, but only 2 were associated with left ventricular hypertrophy. All but 2 false positive defects were reversible, and 6 were located in the right coronary artery segments.

Side effects of the stress test: During dipyridamole infusion, heart rate increased from 78 ± 16 to 90 ± 18 beats/min ($p < 0.001$), and systolic blood pressure decreased from 134 ± 19 to 129 ± 20 mm Hg (p = not significant), whereas diastolic pressure decreased from 77 ± 14 to 72 ± 15 mm Hg ($p < 0.05$). Side effects of the dipyridamole-handgrip stress test were anginal chest pain in 2 cases (both without angiographic evidence of CAD), and dyspnea and dizziness in 1 necessitating a reduction by 20% of the calculated dose of dipyridamole. Hence, the frequency of the dipyridamole-linked side effects was 7%. Aminophylline administration was not needed.

DISCUSSION

Detection of coronary artery disease: In this small study cohort with aortic or mitral heart valvular disease, the prevalence of CAD was 45%, which is somewhat higher than that (32%) in a largely comparable Scandinavian series of 329 patients.[14] These figures of prevalence are suggested to be ideal for noninvasive testing in terms of achieving the best possible benefit from the test.[15] In the current series, all 14 patients (30%) with a negative history of angina pectoris, and a negative finding by MIBI tomography had a negative finding by coronary angiography. If both a positive history of angina pectoris and a positive tomography finding had been used as an indication to cardiac catheterization, no case of significant CAD would have been missed, but this perfect "pick up" would have resulted in 12 "unnecessary" catheterizations (25%).

Detection of vessel stenoses: The overall vessel disease sensitivity (63%) remained lower than in our recent study of patients with known CAD.[11] These differences may be partly explained by the "referral selection bias,"[16] because our results agree excellently with a recent study by Pozzoli et al[17] of 75 patients with an equal frequency of diseased vessels. In our patients, the false positive tomographic vessel findings were "overrepresented" among those with aortic valve disease, but they were only infrequently related to the left ventricular hypertrophy, a condition previously shown to cause defects in thallium scintigraphy in hypertrophic cardiomyopathy.[18]

Technetium-99m isonitrile versus thallium imaging: We used the same-day stress-rest study protocol in MIBI tomography that was proposed to be comparable to the rest-stress or 2-day protocol when the time interval between the injections is >2 hours.[19] Our recent study[11] performed according to the same protocol in coronary patients without valvular heart disease did not show essential differences between MIBI and thallium-201 in terms of diagnostic accuracy, despite a superior image quality obtained with MIBI. In our previous study,[2] using the planar thallium technique in patients with aortic stenosis and a 48% prevalence of CAD, sensitivity (85%) and specificity (86%) were similar to those in the present series, but if the subset of 22 patients with aortic stenosis (50% prevalence of CAD) in the current study is assessed separately, sensitivity and specificity of 91 and 73%, respectively, are obtained. Our previous study of patients with mitral valve stenosis[20] resulted in a slightly higher sensitivity (91%) and a similar specificity (82%) compared with those of the present study.

Dipyridamole-handgrip: Dipyridamole has been suggested to be suited for the detection of reduced coronary vasodilatatory capacity also in the collateralized myocardium.[21] One case of a fatal complication possibly related to the hypotony induced by dipyridamole in a patient with aortic stenosis and cerebral arteriosclerosis was previously reported.[22] In the present study, the frequency of side effects observed with the higher dose of dipyridamole did not exceed that observed previously with lower doses,[2] even though approximately half of our patients presented with critical valve disease. We have suggested that this reasonably low occurrence of side effects is due to the discontinuation of long-acting nitrates and to use of the handgrip exercise in combination with dipyridamole infusion.[11] Both of these procedures may counteract the side effects related to the hypotonic effects of dipyridamole.

In our experience, dipyridamole infusion is the preferable stress method for elderly patients with valvular heart disease who are often unable to perform an adequate exercise test.

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Frequency of Magnetic Resonance Signal Abnormalities of the Brain in Patients Aged <50 Years with Idiopathic Dilated Cardiomyopathy

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Twenty patients with idiopathic dilated cardiomyopathy (IDC) aged <50 years (mean 41) and an age-matched group of 20 healthy volunteers were studied. All subjects were free of cerebrovascular symptoms and risk factors for stroke. Magnetic resonance imaging of the brain, extracranial Doppler ultrasonography, heart catheterization and echocardiography were performed. In patients with IDC, a higher frequency of ventricular enlargement ($p < 0.02$), cortical atrophy ($p < 0.01$) and white matter lesions ($p < 0.05$) was observed. Cerebral infarcts were found in 4 patients ($p < 0.05$) who showed clinically severe limitation of functional capacity (New York Heart Association class III or IV). The extent of cortical atrophy, and the duration of clinical evidence of IDC showed a significant correlation ($p < 0.04$). The data indicate a high incidence of parenchymal abnormalities of the brain in young, neurologically asymptomatic patients with IDC.

(Am J Cardiol 1992;69:1446–1450)

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In patients with idiopathic dilated cardiomyopathy (IDC), impairment of the cerebral blood flow caused by a significant systolic dysfunction, and intracavitary thrombi are suggested to be the pathophysiologic mechanisms leading frequently to diffuse or focal cerebral abnormalities.[1,2] Cerebral infarcts, cortical atrophy, ventricular enlargement and white matter lesions are frequently noted in the elderly, and their incidence is correlated with the number of risk factors for stroke.[3–6] This study assesses the prevalence of cerebral abnormalities in young patients with dilated cardiomyopathy without neurologic symptoms, taking advantage of the high sensitivity of magnetic resonance imaging (MRI).

METHODS

Study patients: The study included 20 consecutive patients (19 men and 1 woman; mean age 41 years, range 18 to 49) with IDC. The diagnosis of IDC was based on chest radiograph, echocardiography, left ventricular angiogram and presence of angiographically normal coronary arteries.[7,8] All patients had some limitation in functional capacity assessed by New York Heart Association (NYHA) classification; 9 were classified as class II, 10 as class III, and 1 as class IV.[9] Duration of cardiac symptoms ranged from 1 to 48 months. Atrial fibrillation was found in 4 patients, and 16 showed sinus rhythm. Fifteen patients received drug therapy (5 digoxin alone, and 10 digoxin plus diuretic agents). No patient was treated with anticoagulants or aspirin. Because patchy subcortical foci of increased signal intensity are frequently identified by MRI in the elderly, we selected only patients aged <50 years who were free of cerebrovascular symptoms by history and neurologic examination. Patients had no evidence of hypertension, diabetes mellitus, hypercholesterolemia, smoking history or other cardiovascular diseases, because these are considered to be major risk factors for stroke. Subjects with a history of head trauma, suggested demyelinating disease or previous cerebrovascular disease, or excessive consumption of alcohol (daily intake of ≥8 ounces of hard liquor, 2 quarts of beer, or >1 quart of wine) were excluded from the study. Therefore, the possibility of multifactorial causation of magnetic resonance signal abnormalities of the brain was reduced to a minimum. The control group comprised 20 healthy volunteers matched for age and sex (19 men and 1 woman; mean age 39 years, range 19 to 49). No control subject had a history of cerebrovascular or car-

diovascular disease, and all had normal physical and neurologic examinations before entering the study.

Equipment and performance: All patients in this study had M-mode and 2-dimensional echocardiograms, using commercially available echocardiographic equipment (SSH-65A, Toshiba, Tokyo, Japan) with a 2.5 MHz transducer. End-diastolic and end-systolic measurements were obtained according to the recommendations of the American Society of Echocardiography.[10] Left and right heart catheterization, and left ventricular and coronary angiography (Advantx L/U-C, General Electric, Milwaukee, Wisconsin) were performed in all patients. Left ventricular angiography was performed in the 30° right anterior oblique projection, and wall motion abnormalities, as well as left ventricular ejection fraction, were analyzed using a computerized system. Mitral regurgitation (if present) was graded during left ventriculography from the visualization of dye in the left atrium as mild (dye just visible), moderate (weak opacification of the atrium, but clearing within 1 or 2 beats after end of injection) or severe (sustained dense opacification of atrium). All patients underwent selective coronary arteriography by means of the Judkins technique. Continuous-wave Doppler examination of the extracranial cerebral arteries, and duplex scanning of the extracranial carotid arteries (Diasonics Vingmed CFM 700, Horten, Norway) were performed in all subjects. Mixed and T2-weighted[11] magnetic resonance images of the brain were obtained using a 1.5 Tesla superconducting magnet (Gyroscan S 15, Philips, Eindhoven, the Netherlands) and the spin-echo technique. The brain was imaged in the axial plane with a slice thickness of 5 mm. A pulsed repetition time (TR) of 1,800 to 2,500 ms, and 2 different echo times (TE) of 30 and 60 ms were used. Furthermore, images were obtained in the sagittal plane with short pulse frequencies (spin-echo, TR/TE 600/30). The matrix was 128 × 256 picture elements. Images were analyzed for cerebral atrophy, ventricular enlargement and signal abnormalities, without knowledge of the clinical diagnosis. Relative volumetric indexes for ventricular enlargements were obtained by calculating a ventricular-to-intracranial cavity ratio, using software routines available with the Philips system. The outer margin of the subarachnoid space and the ventricles were traced on 5 subsequent T2-weighted images beginning at the bottom of the third ventricle. The ventricular-to-intracranial cavity ratio was calculated by dividing the sum of the ventricular volumes by that of the intracranial cavity × 100. White matter lesions were defined as patchy subcortical foci of increased signal intensity on T2-weighted images, according to the criteria of Fazekas et al.[12] Enzyme-linked immunosorbent assays for antibody to Borrelia burgdorferi in serum were determined in both groups.

TABLE I M-Mode Echocardiographic Measurements

	ICD Group	Control Subjects
LV end-diastolic diameter (cm)	6.70 ± 0.75	4.50 ± 0.80
LV end systolic diameter (cm)	5.66 ± 0.80	3.04 ± 0.46
End-diastolic septal wall thickness (cm)	1.21 ± 0.34	0.91 ± 0.17
End-systolic septal wall thickness (cm)	1.17 ± 0.31	1.32 ± 0.21
LV end-diastolic posterior wall thickness (cm)	1.16 ± 0.23	0.94 ± 0.19
LV end-systolic posterior wall thickness (cm)	1.59 ± 0.28	1.38 ± 0.24
RV end-diastolic diameter (cm)	2.58 ± 0.59	1.92 ± 0.43
Left atrial end-systolic diameter (cm)	4.94 ± 0.72	3.18 ± 0.61
Fractional fiber shortening (%)	15.35 ± 6.53	35.21 ± 5.28

Values are mean ± SD.
ICD = idiopathic dilated cardiomyopathy; LV = left ventricular; RV = right ventricular.

Statistical analysis: All data are expressed as mean ± SD. Differences among groups were examined for significance using analysis of variance and the Newman-Keuls multiple-comparison test.[13] Statistical significance was defined as $p \leq 0.05$.

RESULTS

Echocardiographic measurements of patients with IDC are listed in Table I. The 2-dimensional echocardiographic studies did not reveal any intracardiac

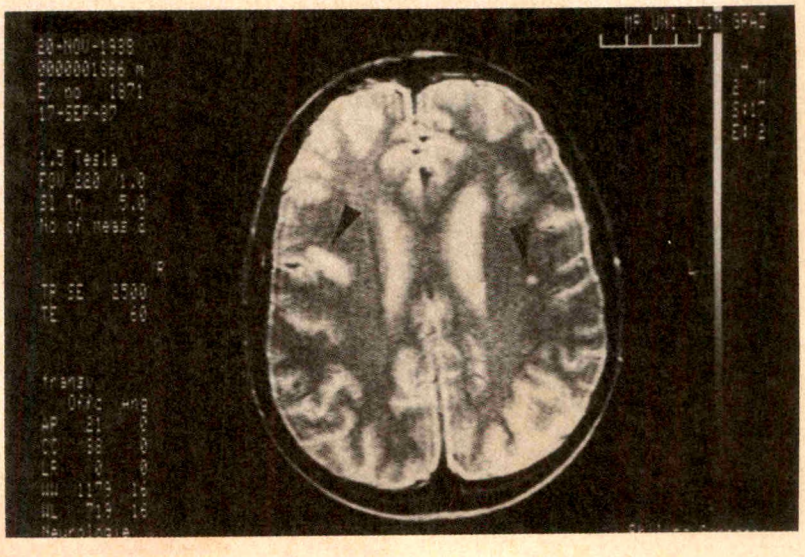


FIGURE 1. Cerebral infarction located in right hemisphere, and white matter lesions in left hemisphere detected by T2-weighted nuclear magnetic resonance imaging (1.5 Tesla; TR = 2,500 ms; and TE = 60 ms). TE = echo time; TR = repetition time.

TABLE II Cerebral Abnormalities in Patients with Idiopathic Dilated Cardiomyopathy Detected by Magnetic Resonance Imaging

	IDC (n = 20)	Control Subjects (n = 20)	p Value
Cerebral infarction	4 (20%)	0 (0%)	<0.05
Ventricular enlargement	11 (55%)	3 (15%)	<0.02
Cortical atrophy	10 (50%)	1 (5%)	<0.01
White matter lesions	6 (30%)	1 (5%)	<0.05
No. of subjects with MRI abnormalities	12 (60%)	3 (15%)	<0.02

IDC = idiopathic dilated cardiomyopathy; MRI = magnetic resonance imaging.

thrombus, mitral valve prolapse or vegetation of the valves. In the control group, echocardiographic results were within the normal range. Left ventricular angiography revealed a mean ejection fraction of 29 ± 5.9% (range 15 to 45) in the IDC group. Mean left ventricular end-diastolic pressure was 18 ± 13 mm Hg, mean pulmonary capillary wedge pressure 17 ± 7.8 mm Hg and mean pulmonary artery pressure 29 ± 13.3 mm Hg. Selective coronary arteriography revealed normal coronary arteries in all patients. Mild mitral regurgitation was observed in 5 patients. Continuous-wave Doppler examination of the extracranial cerebral arteries, and duplex scanning of the extracranial carotid arteries revealed bilateral plaques with <20% stenosis in 3 patients, and unilateral plaque with <20% stenosis in 1 patient. Four patients had MRI evidence of cerebral infarcts (Figure 1) that have remained asymptomatic ($p < 0.05$). Only 1 of these 4 patients had chronic atrial fibrillation, but all had clinically severe limitation in functional capacity (NYHA class III or IV). In these patients, the mean left ventricular ejection fraction was 25 ± 4.8%. There was no correlation between cardiac rhythm and magnetic resonance signal abnormalities (Table II). Three of 4 patients with cerebral infarction had 2 lesions, which were bilateral in 2 cases. All lesions were incomplete territorial infarcts, 2 infarcts were located cortically, and all others involved the cortex and adjacent white matter. MRI of the brain revealed ventricular enlargement in 11 patients and 3 control subjects ($p < 0.02$). Diffuse cortical atrophy (Figure 2) was seen in 10 patients and 1 control subject ($p < 0.01$). Mean ventricular-to-intracranial cavity ratios were 6.2 ± 2.9% in the IDC group and 4.1 ± 1.3% in control subjects ($p < 0.01$). Excluding the 4 patients with cerebral infarcts, there is still a significant increase in ventricular volume and cortical atrophy in the nonstroke IDC group compared with that in control subjects ($p < 0.05$). The correlation between the duration of clinical evidence of IDC and the extent of cortical atrophy was statistically significant ($r = 0.54$; $p < 0.05$). White matter lesions were found in 6 patients and 1 control subject ($p < 0.05$). The white matter lesions were all of the punctate type[12] and ranged in number from 1 to 4 (mean 2.1). In 1 case, both ischemic brain infarct and white matter lesions could be detected. No correlation was found between left ventricular ejection fraction and brain abnormalities. Patients with NYHA class III to IV had a higher incidence of magnetic resonance signal abnormalities of the brain than did those with class II (74 vs 25.8%). Enzyme-linked immunosorbent assays for antibody to Borrelia burgdorferi in serum were normal in both groups.

DISCUSSION

IDC is believed to be a predisposing factor for stroke.[7] Roberts et al[14] studied 152 necropsy patients with IDC and found intracavitary thrombi in 28%, mural endocardial plaques in 22%, and both in 25%. In 115 patients with IDC, Segal et al[15] found history of emboli in 10%. Unverferth[1] reported stroke in 2% of IDC patients. These results are in agreement with those of a Mayo Clinic series[7] in which 4% of patients had history of systemic emboli at the time of diagnosis. All these studies are related to symptomatic embolic events or history of systemic emboli. Therefore, 1 of the main causes of stroke in patients with IDC may be cardiac

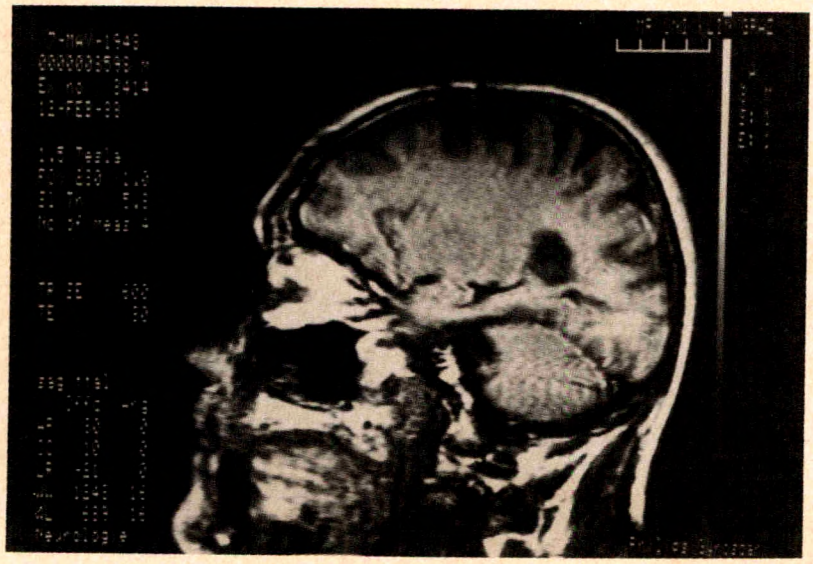


FIGURE 2. Severe cortical atrophy in 45-year-old patient with idiopathic dilated cardiomyopathy (1.5 Tesla; TR = 600 ms; and TE = 30 ms). TE = echo time; TR = repetition time.

embolization.[16] Additional mechanisms such as alterations in hemostatic function, decreased cerebral blood flow and increased plasma concentration of atrial natriuretic peptide may contribute to the increased risk of stroke in patients with IDC.[17–20] Previous studies demonstrated an increased rate of stroke in patients with chronic atrial fibrillation caused by different cardiac diseases.[21–24] The Framingham Study documented the risk of an initial cerebral infarct in patients with chronic atrial fibrillation to be >5 times higher than that in patients with sinus rhythm, corresponding to a yearly incidence of stroke of approximately 4.2%.[25] Fuster et al[7] described systemic emboli in 33% of patients with chronic atrial fibrillation, but in only 14% of those with sinus rhythm of 104 patients with IDC; however, this difference did not reach statistical significance. In agreement with these results, our study suggests that in patients with IDC, silent cerebral infarction occurs in those with sinus rhythm, as well as in those with chronic atrial fibrillation, because 3 (75%) with cerebral infarction showed sinus rhythm, and atrial fibrillation was observed in only 1 (25%). It is noteworthy that only 4 patients in the IDC group showed atrial fibrillation. Brains of IDC patients showed a significant increase of ventricular volumes and cortical atrophy, which may be caused by silent microemboli and chronic severe reduction of the systolic left ventricular function. In 30% of patients with IDC and in 5% of control subjects, white matter lesions[3–6,12,25–28] could be detected by MRI ($p < 0.05$). White matter lesions in T2-weighted images appear to be an early stage of cerebrovascular disease, and are positively correlated with advancing age and the major risk factors for stroke.[3–6,12,25,26,29,30] These lesions represent areas of infarction, demyelination or gliosis without inflammatory cells.[31,32] Impairment of cerebral perfusion, and a significant reduction in flow of the slow flowing compartment due to systolic dysfunction may cause these abnormalities of the white matter. Microemboli may be additional factors in the pathophysiologic mechanism. Recent studies confirm the high incidence of asymptomatic cerebral abnormalities detected by MRI in normal subjects aged >50 years and subjects with well-documented cerebrovascular risk factors. Patients with hypertension, diabetes mellitus, smoking history, hypercholesterolemia, excessive consumption of alcohol, and previous cerebrovascular disease were excluded from our study; thus, the possibility of multifactorial causation of hyperintense white matter foci was kept to a minimum. Recommendations for therapy remain controversial. The Mayo Clinic study[7] documented 3.5 embolic episodes/100 patient years in patients with IDC who were not receiving anticoagulants, and none in those who were receiving such therapy. Sinus rhythm does not appear to be a protective factor for systemic emboli in patients with IDC. In the Copenhagen Atrial Fibrillation Aspirin-Anticoagulation study,[33] the incidence of thromboembolic complications and vascular mortality in patients with chronic atrial fibrillation was significantly lower in the warfarin group than in the aspirin and placebo groups, which did not differ significantly. From this study, it seems reasonable to recommend anticoagulation with warfarin for stroke prophylaxis in chronic nonrheumatic atrial fibrillation. Because the pathophysiologic mechanisms of silent cerebral infarction and white matter lesions in patients with IDC may be the same as those of chronic atrial fibrillation, neurologically intact patients with IDC may represent a therapeutically attractive subgroup for stroke prophylaxis with anticoagulants. However, the data in the present study is small, and final conclusions should await further studies of more patients.

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Although acute hemodynamic studies in a small number of patients with NYHA Class II or III heart failure treated with felodipine have not demonstrated negative inotropic effects, safety in patients with heart failure has not been established. Caution, therefore, should be exercised when using PLENDIL in patients with heart failure or compromised ventricular function, particularly in combination with a beta blocker.

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Elderly Patients or Patients with Impaired Liver Function: Patients over 65 years of age or patients with impaired liver function may have elevated plasma concentrations of felodipine and may therefore respond to lower doses of PLENDIL. These patients should have their blood pressure monitored closely during dosage adjustment of PLENDIL and should rarely require doses above 10 mg. (See CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION.)

Peripheral Edema: Peripheral edema, generally mild and not associated with generalized fluid retention, was the most common adverse event in the clinical trials. The incidence of peripheral edema was both dose- and age-dependent. Frequency of peripheral edema ranged from about 10 percent in patients under 50 years of age taking 5 mg daily to about 30 percent in those over 60 years of age taking 20 mg daily. This adverse effect generally occurs within 2-3 weeks of the initiation of treatment.

Information for Patients: Patients should be instructed to take PLENDIL whole and not to crush or chew the tablets. They should be told that mild gingival hyperplasia (gum swelling) has been reported. Good dental hygiene decreases its incidence and severity.

NOTE: As with many other drugs, certain advice to patients being treated with PLENDIL is warranted. This information is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects.

Drug Interactions: ***Beta-Blocking Agents:*** A pharmacokinetic study of felodipine in conjunction with metoprolol demonstrated no significant effects on the pharmacokinetics of felodipine. The AUC and C_{max} of metoprolol, however, were increased approximately 31 and 38 percent, respectively. In controlled clinical trials, however, beta-blockers including metoprolol were concurrently administered with felodipine and were well tolerated.

Cimetidine: In healthy subjects pharmacokinetic studies showed an approximately 50 percent increase in the area under the plasma concentration time curve (AUC) as well as the C_{max} of felodipine when given concomitantly with cimetidine. It is anticipated that a clinically significant interaction may occur in some hypertensive patients. Therefore, it is recommended that low doses of PLENDIL be used when given concomitantly with cimetidine.

Digoxin: When given concomitantly with felodipine the peak plasma concentration of digoxin was significantly increased. There was, however, no significant change in the AUC of digoxin.

Other Concomitant Therapy: In healthy subjects there were no clinically significant interactions when felodipine was given concomitantly with indomethacin or spironolactone.

Interaction with Food: See CLINICAL PHARMACOLOGY, *Pharmacokinetics and Metabolism.*

Carcinogenesis, Mutagenesis, Impairment of Fertility: In a two-year carcinogenicity study in rats fed felodipine at doses of 7.7, 23.1 or 69.3 mg/kg/day (up to 28 times* the maximum recommended human dose on a mg/m² basis), a dose-related increase in the incidence of benign interstitial cell tumors of the testes (Leydig cell tumors) was observed in treated male rats. These tumors were not observed in a similar study in mice at doses up to 138.6 mg/kg/day (28* times the maximum recommended human dose on a mg/m² basis). Felodipine, at the doses employed in the two-year rat study, has been shown to lower testicular testosterone and to produce a corresponding increase in serum luteinizing hormone in rats. The Leydig cell tumor development is possibly secondary to these hormonal effects which have not been observed in man.

In this same rat study a dose-related increase in the incidence of focal squamous cell hyperplasia compared to control was observed in the esophageal groove of male and female rats in all dose groups. No other drug-related esophageal or gastric pathology was observed in the rats or with chronic administration in mice and dogs. The latter species, like man, has no anatomical structure comparable to the esophageal groove.

Felodipine was not carcinogenic when fed to mice at doses of up to 138.6 mg/kg/day (28 times* the maximum recommended human dose on a mg/m² basis) for periods of up to 80 weeks in males and 99 weeks in females.

Felodipine did not display any mutagenic activity *in vitro* in the Ames microbial mutagenicity test or in the mouse lymphoma forward mutation assay. No clastogenic potential was seen *in vivo* in the mouse micronucleus test at oral doses up to 2500 mg/kg (506 times* the maximum recommended human dose on a mg/m² basis) or *in vitro* in a human lymphocyte chromosome aberration assay.

A fertility study in which male and female rats were administered doses of 3.8, 9.6 or 26.9 mg/kg/day showed no significant effect of felodipine on reproductive performance.

Pregnancy: ***Pregnancy Category C:*** *Teratogenic Effects:* Studies in pregnant rabbits administered doses of 0.46, 1.2, 2.3 and 4.6 mg/kg/day (from 0.4 to 4 times* the maximum recommended human dose on a mg/m² basis) showed digital anomalies consisting of reduction in size and degree of ossification of the terminal phalanges in the fetuses. The frequency and severity of the changes appeared dose-related and were noted even at the lowest dose. These changes have been shown to occur with other members of the dihydropyridine class and are possibly a result of compromised uterine blood flow. Similar fetal anomalies were not observed in rats given felodipine.

In a teratology study in cynomolgus monkeys no reduction in the size of the terminal phalanges was observed but an abnormal position of the distal phalanges was noted in about 40 percent of the fetuses.

Nonteratogenic Effects: A prolongation of parturition with difficult labor and an increased frequency of fetal and early postnatal deaths were observed in rats administered doses of 9.6 mg/kg/day (4 times* the maximum human dose on a mg/m² basis) and above.

Significant enlargement of the mammary glands in excess of the normal enlargement for pregnant rabbits was found with doses greater than or equal to 1.2 mg/kg/day (equal to the maximum human dose on a mg/m² basis). This effect occurred only in pregnant rabbits and regressed during lactation. Similar changes in the mammary glands were not observed in rats or monkeys.

There are no adequate and well-controlled studies in pregnant women. If felodipine is used during pregnancy, or if the patient becomes pregnant while taking this drug, she should be apprised of the potential hazard to the fetus, possible digital anomalies of the infant, and the potential effects of felodipine on labor and delivery, and on the mammary glands of pregnant females.

Nursing Mothers: It is not known whether this drug is secreted in human milk and because of the potential for serious adverse reactions from felodipine in the infant, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: In controlled studies in the United States and overseas approximately 3000 patients were treated with felodipine as either the extended-release or the immediate-release formulation.

The most common clinical adverse experiences reported with PLENDIL® (Felodipine, MSD) administered as monotherapy in all settings and with all dosage forms of felodipine were peripheral edema and headache. Peripheral edema was generally mild, but it was age- and dose-related and resulted in discontinuation of therapy in about 4 percent of the enrolled patients. Discontinuation of therapy due to any clinical adverse experience occurred in about 9 percent of the patients receiving PLENDIL, principally for peripheral edema, headache, or flushing.

Adverse experiences that occurred with an incidence of 1.5 percent or greater during monotherapy with PLENDIL without regard to causality are compared to placebo in the table below.

Percent of Patients with Adverse Effects in Controlled Trials of PLENDIL as Monotherapy (Incidence of discontinuations shown in parentheses)

Adverse Effect	PLENDIL % N = 730		Placebo % N = 283
Peripheral Edema	22.3	(4.2)	3.5
Headache	18.6	(2.1)	10.6
Flushing	6.4	(1.0)	1.1
Dizziness	5.8	(0.8)	3.2
Upper Respiratory Infection	5.5	(0.1)	1.1
Asthenia	4.7	(0.1)	2.8
Cough	2.9	(0.0)	0.4
Paresthesia	2.5	(0.1)	1.8
Dyspepsia	2.3	(0.0)	1.4
Chest Pain	2.1	(0.1)	1.4
Nausea	1.9	(0.8)	1.1
Muscle Cramps	1.9	(0.0)	1.1
Palpitation	1.8	(0.5)	2.5
Abdominal Pain	1.8	(0.3)	1.1
Constipation	1.6	(0.1)	1.1
Diarrhea	1.6	(0.1)	1.1
Pharyngitis	1.6	(0.0)	0.4
Rhinorrhea	1.6	(0.0)	0.0
Back Pain	1.6	(0.0)	1.1
Rash	1.5	(0.1)	1.1

*Based on patient weight of 50 kg

In the two dose response studies using PLENDIL® (Felodipine, MSD) as monotherapy, the following table describes the incidence (percent) of adverse experiences that were dose-related:

Adverse Effect	Placebo N = 121	5.0 mg N = 72	10.0 mg N = 123	20 mg N = 50
Peripheral Edema	2.5	13.9	19.5	36.0
Palpitation	0.8	0.0	2.4	12.0
Headache	12.4	11.1	18.7	28.0
Flushing	0.0	2.8	8.1	20.0

In addition, adverse experiences that occurred in 0.5 up to 1.5 percent of patients who received PLENDIL in all controlled clinical studies (listed in order of decreasing severity within each category) and serious adverse events that occurred at a lower rate or were found during marketing experience (those lower rate events are in italics) were: *Body as a Whole:* Facial edema, warm sensation; *Cardiovascular:* Tachycardia, *myocardial infarction, hypotension, syncope, angina pectoris,* arrhythmia; *Digestive:* Vomiting, dry mouth, flatulence; *Hematologic: Anemia; Musculoskeletal:* Arthralgia, arm pain, knee pain, leg pain, foot pain, hip pain, myalgia; *Nervous/Psychiatric:* Depression, anxiety disorders, insomnia, irritability, nervousness, somnolence; *Respiratory:* Bronchitis, influenza, sinusitis, dyspnea, epistaxis, respiratory infection, sneezing; *Skin:* Contusion, erythema, urticaria; *Urogenital:* Decreased libido, impotence, urinary frequency, urinary urgency, dysuria.

Felodipine, as an immediate release formulation, has also been studied as monotherapy in 680 patients with hypertension in U.S. and overseas controlled clinical studies. Other adverse experiences not listed above and with an incidence of 0.5 percent or greater include: *Body as a Whole:* Fatigue; *Digestive:* Gastrointestinal pain; *Musculoskeletal:* Arthritis, local weakness, neck pain, shoulder pain, ankle pain; *Nervous/Psychiatric:* Tremor; *Respiratory:* Rhinitis; *Skin:* Hyperhidrosis, pruritus; *Special Senses:* Blurred vision, tinnitus; *Urogenital:* Nocturia.

Gingival Hyperplasia: Gingival hyperplasia, usually mild, occurred in <0.5 percent of patients in controlled studies. This condition may be avoided or may regress with improved dental hygiene. (See PRECAUTIONS, *Information for Patients.*)

Clinical Laboratory Test Findings: ***Serum Electrolytes:*** No significant effects on serum electrolytes were observed during short- and long-term therapy (see CLINICAL PHARMACOLOGY, *Renal Endocrine Effects*).

Serum Glucose: No significant effects on fasting serum glucose were observed in patients treated with PLENDIL in the U.S. controlled study.

Liver Enzymes: One of two episodes of elevated serum transaminases decreased once drug was discontinued in clinical studies; no follow-up was available for the other patient.

OVERDOSAGE: Oral doses of 240 mg/kg and 264 mg/kg in male and female mice, respectively, and 2390 mg/kg and 2250 mg/kg in male and female rats, respectively, caused significant lethality.

In a suicide attempt, one patient took 150 mg felodipine together with 15 tablets each of atenolol and spironolactone and 20 tablets of nitrazepam. The patient's blood pressure and heart rate were normal on admission to hospital; he subsequently recovered without significant sequelae.

Overdosage might be expected to cause excessive peripheral vasodilation with marked hypotension and possibly bradycardia.

If severe hypotension occurs, symptomatic treatment should be instituted. The patient should be placed supine with the legs elevated. The administration of intravenous fluids may be useful to treat hypotension due to overdosage with calcium antagonists. In case of accompanying bradycardia, atropine (0.5-1 mg) should be administered intravenously. Sympathomimetic drugs may also be given if the physician feels they are warranted.

It has not been established whether felodipine can be removed from the circulation by hemodialysis.

DOSAGE AND ADMINISTRATION: The recommended initial dose is 5 mg once a day. Therapy should be adjusted individually according to patient response, generally at intervals of not less than two weeks. The usual dosage range is 5-10 mg once daily. The maximum recommended daily dose is 20 mg once a day. That dose in clinical trials showed an increased blood pressure response but a large increase in the rate of peripheral edema and other vasodilatory adverse events (see ADVERSE REACTIONS). Modification of the recommended dosage is usually not required in patients with renal impairment.

PLENDIL should be swallowed whole and not crushed or chewed.

Use in the Elderly or Patients with Impaired Liver Function: Patients over 65 years of age or patients with impaired liver function, because they may develop higher plasma concentrations of felodipine, should have their blood pressure monitored closely during dosage adjustment (see PRECAUTIONS). In general, doses above 10 mg should not be considered in these patients.

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Ventricular Arrhythmias in Dilated Cardiomyopathy as an Independent Prognostic Hallmark

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Prevalence and characteristics of ventricular arrhythmias (VA) on Holter monitoring were evaluated in 218 patients with invasively documented idiopathic dilated cardiomyopathy to clarify their relation to pump dysfunction, and their prognostic role. VA were observed in 205 patients (94%) and were high grade (ventricular pairs or tachycardia) in 130 (60%). No simple or multiform ventricular premature complexes were present in 88 patients (group 1; 41%), ventricular pairs in 63 (group 2; 32%), and ventricular tachycardia in 67 (group 3; 27%). Only echocardiographic right ventricular dimensions ($p < 0.05$) and prevalence of VA during effort (8% in group 1, 15% in group 2, and 14% in group 3; $p = 0.0005$) differed significantly between groups. VA severity, and number of ventricular premature beats and tachycardia episodes were not correlated to right/left ventricular dimensions and pump function indexes. During a mean follow-up of 29 ± 16 months, 27 patients died from cardiac events, and 16 received transplants. Three-year survival probability was lower in groups 2 (0.82) and 3 (0.81) than in group 1 (0.94).

By Cox multivariate analysis, VA severity ($p < 0.01$) was a major independent predictor of prognosis after markers of ventricular dysfunction such as left ventricular ejection fraction ($p < 0.001$) and stroke work index ($p < 0.001$).

(Am J Cardiol 1992;69:1451–1457)

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Idiopathic dilated cardiomyopathy (IDC) has traditionally been considered a disease with a severe prognosis often leading to sudden death.[1–3] Recent studies reported a less unfavorable outcome.[4,5] Among the many undefined aspects of IDC, the role of ventricular arrhythmias (VA) represents a continuing enigma. Whereas a high prevalence of complex VA[6–15] has uniformly been reported in IDC, their clinical relevance, relation to pump function, and prognostic role are still unresolved issues.[6–8,10–12,14] In some studies, VA had no predictive value for cardiac death,[6,7,10,11] whereas in others they were major risk indicators for sudden death[8,14,15] or global cardiac mortality.[3,9,12,13]

This study evaluates prevalence, characteristics and clinical significance of VA detected by Holter monitoring in 218 patients with IDC studied in the late 1980s and assesses their prognostic significance.

METHODS

Between January 1986 and March 1990, 218 consecutive patients with IDC from 15 different centers were prospectively enrolled in a multicenter registry on the natural history of IDC. Patients referred to the participating centers because of heart failure, high-grade VA or severe reduction of ventricular function (echocardiographic left ventricular fractional shortening <20%) of unknown etiology, or a combination, underwent a noninvasive evaluation including physical examination, 12-lead electrocardiogram, M-mode and 2-dimensional echocardiography, 24-hour Holter monitoring and exercise stress testing.

The clinical suspicion of IDC was confirmed invasively in each patient by demonstrating: (1) absence of significant coronary artery disease (>50% reduction in luminal diameter of major coronary artery branch) at coronary angiography, (2) absence of specific heart muscle disease or active myocarditis at endomyocardial biopsy, and (3) reduced left ventricular ejection fraction (<55%) at cineangiography.

At 2 centers actively involved in a cardiac transplantation program, patients with end-stage IDC who were specifically referred for heart replacement and entered in the transplant waiting list were not included in this series.

All patients were entered in the study after completion of noninvasive and invasive evaluations performed in close temporal relation (<1 month).

TABLE I Laboratory Findings in 218 Patients with Dilated Cardiomyopathy

Presenting symptoms	
Dyspnea	168 (77%)
Palpitations	85 (39%)
Chest pain	30 (13%)
Syncope	7 (3%)
Fatigue	99 (45%)
Heart failure	107 (47%)
NYHA class I	49 (22%)
NYHA class II	80 (37%)
NYHA class III	62 (22%)
NYHA class IV	26 (12%)
Surface electrocardiogram	
Sinus rhythm	190 (87%)
Atrial fibrillation	25 (11%)
1° atrioventricular block	41 (21%)
Left ventricular hypertrophy	53 (25%)
Left anterior hemiblock	23 (11%)
Right bundle branch block	8 (4%)
Left bundle branch block	58 (27%)
Right bundle branch block + left anterior hemiblock	4 (2%)
Exercise stress test	
Functional capacity	
Estimated metabolic equivalents	6 ± 4
Blood pressure increase (mm Hg)	39 ± 25
Exercise duration (min)	9 ± 4
Ventricular arrhythmias	
Total	62 (37%)
Ventricular premature complexes	39 (23%)
Ventricular pairs	18 (11%)
Ventricular tachycardia	5 (3%)

NYHA = New York Heart Association.

Functional status was classified according to New York Heart Association criteria.

Echocardiographic measurements were obtained according to previously published standards[16] and normalized for body surface area. All M-mode measurements were derived from the 2-dimensional parasternal long- and short-axis views; care was taken to select an orthogonal plane to the ultrasound beam.

Left- and right-sided heart catheterizations were performed with fluid-filled catheters and a low-volume displacement transducer. Ventricular pressure recordings were not consistent with a restrictive pattern in any patient. Cardiac output was measured with the thermodilution method. Left ventricular angiography was performed in the 30° right anterior oblique projection; the mean normal value for left ventricular ejection fraction in the participating hemodynamic laboratories was 72 ± 8%; thus, 56% (mean normal value −2 SD) was chosen as the lower normality range value. No patient had angiographic evidence of severe mitral regurgitation. Selective coronary angiography was performed according to Judkins' technique.

Right ventricular endomyocardial biopsy was performed through the right femoral vein with King's College bioptome or through the right internal jugular vein with Caves' bioptome. In a minority of cases, left ventricular endomyocardial biopsy was performed. In each biopsy procedure, ≥4 tissue specimens were obtained and processed for histologic diagnosis; Dallas criteria[17] were used to rule out myocarditis.

When clinically feasible, patients performed a symptom-limited exercise stress test in the upright position on a bicycle cycloergometer with 25 W steps every 3 minutes, or 10 W steps every minute. VA were considered related to effort if in the absence of VA on the baseline pre-exercise electrocardiographic tracing ≥5 ventricular premature complexes occurred after the beginning of testing through the recovery phase. Baseline Holter monitoring was performed for ≥24 hours in all cases. VA were classified as follows: group 1 — nonrepetitive VA (no, simple or multiform ventricular premature complexes); group 2 — ventricular pairs (2 consecutive ventricular premature complexes); and group 3 — ventricular tachycardia (≥3 ventricular premature complexes in succession).

Sustained ventricular tachycardia was defined as an episode of tachycardia lasting >30 seconds and not self-terminating. The total number of ventricular premature complexes in 24 hours, mean hourly frequency and total number of ventricular pairs in 24 hours were calculated. The number of episodes of ventricular tachycardia in 24 hours, rate and number of beats/episode were also evaluated.

At the time of baseline evaluation, 131 patients (60%) were receiving digitalis, 170 (78%) diuretics, 60 (27%) angiotensin-converting enzyme inhibitors, 14 (6%) β blockers and 45 (21%) antiarrhythmic agents (amiodarone in 31 [14%] and other agents in 14 [7%]); 30 patients (14%) were receiving no therapy.

The study began after completion of the baseline evaluation and terminated on December 1990, or at death or transplantation.

Circumstances of death were investigated by interviewing the next of kin, friends or physician. Classification of the type of death was based on evaluation of the state of circulation immediately before death.[18]

Statistical analysis: Continuous data are expressed as mean ± SD.

Where appropriate, Student's t test for unpaired data, or 1-way analysis of variance and post hoc Scheffe's test were used to assess statistically significant differences. Holter parameters were correlated to echocardiographic and hemodynamic indexes by linear regression analysis.

Product limit survival was calculated with Kaplan-Meier curves, and differences between curves were assessed by the Cox-Mantel test. Cox proportional hazards model was used to analyze the relation between survival and prognostic indexes. The Statistical Package for the Social Science Program (SPSS Inc., Chicago, Illinois) and Biomedical Computer Program (BMPD Statistical Software Inc., Los Angeles, California) softwares were used. A p value <0.05 was considered significant.

RESULTS

There were 161 men (74%) and 57 women (26%) (mean age 41 ± 12 years, range 8 to 61) in the study.

The clinical, electrocardiographic, exercise test, echocardiographic and hemodynamic findings at entry in the study are summarized in Tables I and II. Sinus rhythm was present in 190 patients (87%), and chronic

atrial fibrillation in 25 (11%); 3 patients had a permanent pacemaker.

Atrial premature complexes were detected at Holter monitoring in 116 patients (53%), and the median number in 24 hours was 46.5 (mean 275 ± 1,003, range 2 to 8,652). Paroxysmal atrial fibrillation was detected in 2 patients, and paroxysmal atrial flutter in 1.

Prevalence and characteristics of ventricular arrhythmias: VA were present in 205 patients (94%). The median number of ventricular premature complexes in 24 hours was 547 (mean 3,224 ± 6,741, range 1 to 44,000); ventricular premature complexes were infrequent (<500/24 hours) in 97 patients (47%), and frequent (≥500/24 hours) in 108 (53%). In all, 117 patients (54%) had ventricular pairs, with a median number in 24 hours of 8 (mean 46 ± 195; range 1 to 2,213); 79 patients had <20, and 38 patients had ≥20. In 67 patients (31%), a total of 855 episodes of ventricular tachycardia were recorded (median 2, mean 13 ± 58, range 1 to 465 episodes/patient in 24 hours); 25 patients had only 1 episode in 24 hours, 35 had 2 to 10 episodes, and 7 had >10 episodes. All episodes were nonsustained (7 ± 6 beats, range 3 to 33), and none were noticed by patients. The rate of ventricular tachycardia episodes ranged from 70 to 250 beats/min (mean 155 ± 36).

VA during effort were observed in 62 of 168 patients (37%) tested; ventricular tachycardia caused interruption of the test in 5 cases (3%). Ventricular pairs during effort occurred in 18 patients (11%), whereas ventricular premature complexes alone were observed in 39 (23%) and in association with ventricular pairs or tachycardia in 13; they were monofocal in 33, and multifocal in 19.

TABLE II Echocardiographic and Hemodynamic Findings in 218 Patients with Dilated Cardiomyopathy

Echocardiography	
Left atrial dimension index	24 ± 5 mm/m^2
Right ventricular diameter index	13 ± 5 mm/m^2
Left ventricular end-diastolic diameter index	39 ± 7 mm/m^2
Left ventricular end-systolic diameter index	34 ± 7 mm/m^2
Left ventricular fractional shortening	15 ± 6%
Left ventricular ejection fraction	30 ± 10%
Thickening of interventricular septum	13 ± 12%
Thickening of posterior wall	27 ± 19%
Radius to posterior wall thickness ratio	4 ± 1
Hemodynamics	
Mean right atrial pressure	5 ± 4 mm Hg
Right ventricular end-diastolic pressure	6 ± 5 mm Hg
Mean pulmonary artery pressure	22 ± 11 mm Hg
Pulmonary capillary wedge pressure	15 ± 9 mm Hg
Left ventricular end-diastolic pressure	16 ± 11 mm Hg
Mean arterial pressure	89 ± 15 mm Hg
Cardiac index	3 ± 1 L/min/m^2
Stroke volume index	41 ± 18 ml/min/m^2
Left ventricular stroke work index	41 ± 22 gm/m^2
Left ventricular ejection fraction	30 ± 11%

Ventricular arrhythmias and ventricular function: According to severity of VA, 88 patients (40%) were in group 1, 63 (29%) in group 2, and 67 (31%) in group 3.

There were no significant differences between the groups in age, sex, duration of illness, symptoms at entry in the study, and New York Heart Association functional class. Forty-five patients (21%) were receiving maintenance antiarrhythmics; 31 were receiving amiodarone (12 in group 1, 12 in group 2, and 7 in group 3; p = not significant [NS]).

TABLE III Echocardiographic, Hemodynamic and Stress Findings According to Severity of Ventricular Arrhythmias

	Group 1 (n = 88)	Group 2 (n = 63)	Group 3 (n = 67)	p Value
Echocardiography				
Left atrial dimension index	24 ± 6 mm/m^2	24 ± 5 mm/m^2	23 ± 6 mm/m^2	NS
Right ventricular diameter index	12 ± 4 mm/m^2	14 ± 5 mm/m^2	11 ± 5 mm/m^2	<0.05*
Left ventricular end-diastolic diameter index	40 ± 8 mm/m^2	39 ± 5 mm/m^2	39 ± 7 mm/m^2	NS
Left ventricular end-systolic diameter index	34 ± 8 mm/m^2	34 ± 5 mm/m^2	33 ± 7 mm/m^2	NS
Left ventricular fractional shortening	16 ± 7%	15 ± 6%	15 ± 5%	NS
Left ventricular ejection fraction	31 ± 10%	29 ± 10%	29 ± 10%	NS
Thickening of interventricular septum	15 ± 13%	13 ± 14%	11 ± 11%	NS
Thickening of posterior wall	29 ± 20%	25 ± 17%	27 ± 18%	NS
Radius to posterior wall thickness ratio	4 ± 1%	4 ± 1%	4 ± 1%	NS
Cardiac catheterization				
Mean right atrial pressure	5 ± 3 mm Hg	5 ± 4 mm Hg	5 ± 5 mm Hg	NS
Right ventricular end-diastolic pressure	6 ± 3 mm Hg	6 ± 4 mm Hg	6 ± 6 mm Hg	NS
Mean pulmonary artery pressure	21 ± 10 mm Hg	24 ± 11 mm Hg	21 ± 11 mm Hg	NS
Pulmonary capillary wedge pressure	14 ± 8 mm Hg	17 ± 10 mm Hg	15 ± 9 mm Hg	NS
Left ventricular end-diastolic pressure	15 ± 10 mm Hg	18 ± 12 mm Hg	17 ± 10 mm Hg	NS
Mean arterial pressure	92 ± 17 mm Hg	86 ± 13 mm Hg	88 ± 16 mm Hg	NS
Cardiac index	3 ± 1 L/min/m^2	3 ± 1 L/min/m^2	3 ± 1 L/min/m^2	NS
Stroke volume index	43 ± 20 ml/min/m^2	39 ± 16 ml/min/m^2	39 ± 15 ml/min/m^2	NS
Left ventricular stroke work index	47 ± 24 g/m^2	38 ± 21 g/m^2	38 ± 20 g/m^2	NS
Left ventricular ejection fraction	32 ± 11%	28 ± 10%	28 ± 12%	NS
Exercise stress test				
Estimated metabolic equivalents	6 ± 2	5 ± 2	6 ± 2	NS
Blood pressure increase	40 ± 25 mm Hg	39 ± 27 mm Hg	35 ± 23 mm Hg	NS
Exercise duration	9 ± 4 minutes	8 ± 4 minutes	10 ± 4 minutes	NS

*Scheffe's test: group 2 vs groups 1 and 3.
NS = not significant.

TABLE IV Three-Year Survival Probability According to Severity of Ventricular Arrhythmias in 218 Patients with Dilated Cardiomyopathy

	No. of Pts.	Cardiac Death: All Causes	Cardiac Death: Heart Failure	Cardiac Death: Sudden Death
Group 1 (deaths)	88	0.94 (4)	0.98 (1)	0.96 (3)
Group 2 (deaths)	63	0.82 (11)	0.89 (7)	0.92 (4)
Group 3 (deaths)	67	0.81 (12)*	0.89 (6)	0.93 (5)
Mantel-Cox test for comparison among survival curves		$p < 0.05$	$p < 0.05$	NS

*1 patient died of pulmonary embolism confirmed at autopsy.
Significant differences between group 1 and groups 2 and 3.
NS = not significant.

Echocardiographic, hemodynamic and exercise stress test findings in the 3 groups are summarized in Table III. Weakly significant differences were found between echocardiographic right ventricular end-diastolic diameter index in group 2 and those in groups 1 and 3 ($p < 0.05$; Scheffe's test). Patients with high-grade VA during Holter monitoring had VA more frequently during exercise testing (8% in group 1, 15% in group 2, and 14% in group 3; $p = 0.0005$). Ventricular premature complexes alone occurred in 12 patients (18%) in group 1, 17 (42%) in group 2, and 10 (27%) in group 3 ($p < 0.05$). Ventricular pairs occurred in 2 patients (3%) in group 1, 7 (15%) in group 2, and 9 (20%) in group 3 ($p < 0.05$), whereas ventricular tachycardia was observed in no patient in group 1, 1 (2%) in group 2, and 4 (8%) in group 3 ($p < 0.05$).

By linear regression analysis, Holter parameters (VA severity, and total numbers of ventricular premature complexes, pairs and tachycardia episodes) showed no significant relation to echocardiographic and hemodynamic indexes of ventricular dimension (left and right ventricular end-diastolic diameter indexes) and function (left ventricular ejection fraction, cardiac index, and pulmonary capillary wedge, right ventricular end-diastolic and mean right atrial pressures).

Follow-up data: In December 1990, mean follow-up was 29 ± 16 months (range 15 days to 68 months); minimum follow-up for nontransplant surviving patients was 9 months. Seven patients were lost during follow-up, and 3 died from noncardiac causes; 16 underwent heart transplantation.

There were 27 cardiac deaths; 14 heart failures (52%) and 12 sudden deaths (44%); another patient died suddenly, but massive pulmonary embolism (4%) was documented at autopsy. Kaplan-Meier survival curve with respect to cardiac death is shown in Figure 1.

Product limit survival at 12, 24 and 36 months was 93, 87 and 86%, respectively; mean time to death was 10 ± 8 months. Comparing mode of death in relation to severity of VA (Table IV and Figure 2), a higher mortality from heart failure, but not from sudden death was found in groups 2 and 3 than in group 1.

Conversely, analyzing VA according to cause of death, patients dying from heart failure (n = 14) had a similar pattern to that of those dying suddenly (n = 12); ≥500 ventricular premature complexes were present in 43% of those dying from heart failure compared with 42% of those dying suddenly, whereas 43 and 42%, respectively, had ventricular tachycardia. The mean numbers of ventricular premature complexes were 2,262 ± 5,187 in patients dying from heart failure, and 3,719 ± 5,286 in those dying suddenly (p = NS), the mean numbers of ventricular pairs were 8 ± 5 and 33 ± 73 (p = NS), respectively, and the mean numbers of ventricular tachycardia episodes were 3 ± 2 and 2 ± 1 (p = NS), respectively.

Variables significant by Cox univariate analysis for global mortality, heart failure and sudden death are shown in Table V. No variable related to actual treatment (digitalis, angiotensin-converting enzyme inhibitors or antiarrhythmic agents) was significant.

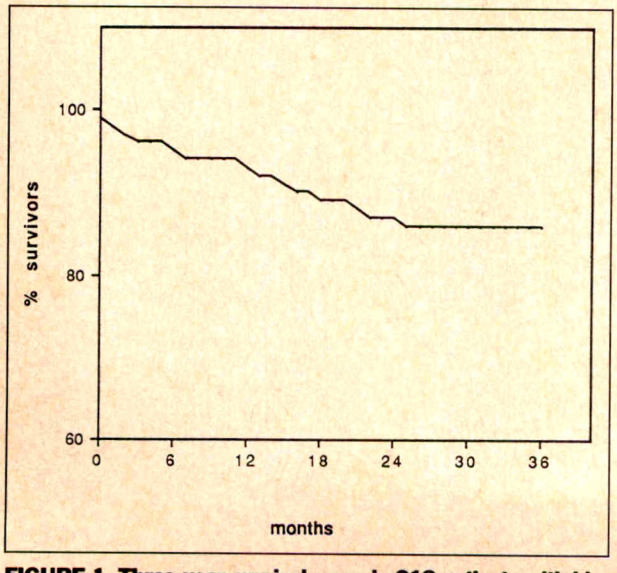


FIGURE 1. Three-year survival curve in 218 patients with idiopathic dilated cardiomyopathy (cardiac mortality).

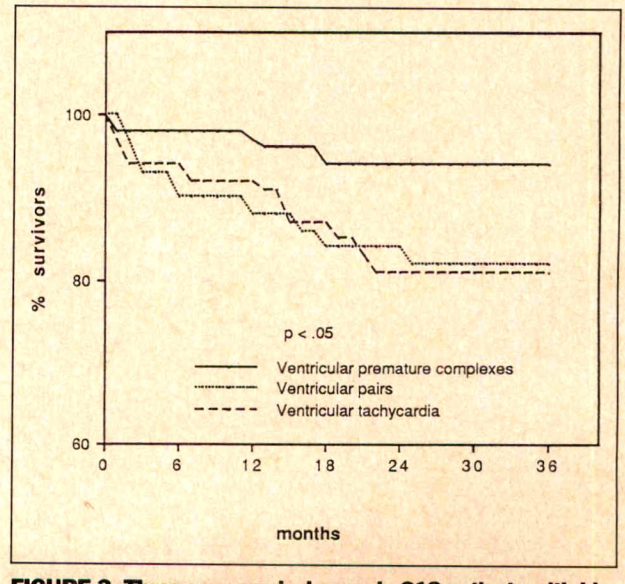


FIGURE 2. Three-year survival curve in 218 patients with idiopathic dilated cardiomyopathy according to ventricular arrhythmia severity at baseline Holter monitoring (cardiac mortality).

The first multivariate regression analysis was performed in the 13 variables marked with an asterisk in Table V, and complete data were available for 164 cases. The major independent determinants of cardiac death were left ventricular stroke work index ($p < 0.001$), VA severity group ($p < 0.01$), and left ventricular end-systolic ($p < 0.01$) and right ventricular ($p < 0.01$) end-diastolic diameter indexes.

The second multivariate analysis included only 6 of the aforementioned significant variables to decrease the likelihood of spurious associations (New York Heart Association functional class, angiographic left ventricular ejection fraction, VA severity group, mean pulmonary artery pressure, left ventricular end-diastolic pressure and cardiac index). Complete data were available in 208 patients. Left ventricular ejection fraction ($p < 0.001$), cardiac index ($p < 0.05$) and VA severity group ($p < 0.05$) were independent predictors of cardiac death in this model.

Because of the univariate analysis results and the low event rate, a separate multivariate analysis for heart failure or sudden death was not performed.

TABLE V Cox Univariate Analysis

	No. of Cases	p Value of Cardiac Deaths: All Causes	Heart Failure	Sudden Death
Right ventricular end-diastolic pressure	189	0.0001	0.0001	NS
Left ventricular ejection fraction*	218	0.0001	0.0008	0.04
Mean capillary wedge pressure*	210	0.0001	0.0001	NS
Left ventricular stroke work index*	198	0.0001	0.0002	NS
Mean pulmonary artery pressure*	214	0.0002	0.0001	NS
Mean right atrial pressure*	212	0.0004	0.0001	NS
Heart failure signs*	218	0.0007	0.008	0.03
Stroke volume index	215	0.001	0.003	NS
Left ventricular end-diastolic pressure*	213	0.002	0.0001	NS
Cardiac index*	215	0.003	0.009	NS
Right ventricular diameter*	187	0.003	0.008	NS
Left ventricular fractional shortening*	206	0.005	0.003	NS
Arrhythmia severity group*	218	0.008	0.03	NS
Left ventricular end-systolic diameter index*	206	0.01	0.02	NS
NYHA class*	218	0.02	0.03	NS
Atrial premature beats	216	0.03	0.003	NS
Mean aortic pressure	214	0.04	0.01	NS
Left atrial diameter index	205	0.07	0.004	NS

*Variables entered in Cox multivariate analysis.
NS = not significant; NYHA = New York Heart Association.

DISCUSSION

VA are reported to be extremely frequent in congestive heart failure and particularly in patients with IDC.[19] Several investigators examined VA in IDC with controversial results. In those studies, the number of patients was often relatively small, and diagnostic criteria were very heterogeneous,[3,6–15] whereas statistical methods to predict prognosis varied widely.

The present multicenter study examined a large number of patients with strict entry criteria including coronary angiography and endomyocardial biopsy; thus, the diagnosis of IDC was uniformly accurate. This study confirmed a high frequency of VA in IDC patients; Holter monitoring detected ventricular premature complexes in 94%, which is consistent with the results of previous studies.[3,8,10,14] Prevalence of complex VA (multiform ventricular premature complexes, pairs and tachycardia) was also found to be in the range previously reported (80 to 95%).[3,6,8,12]

Despite the frequent detection of high-grade VA, most patients with IDC are usually asymptomatic during Holter monitoring[6–8]; in our series, symptoms were present in no recorded episode of nonsustained ventricular tachycardia.

Holter monitoring was performed during antiarrhythmic treatment in 21% of cases, equally distributed among the groups with different severity of VA and thus minimizing the risk of bias. Although it has been suggested that a specific antiarrhythmic treatment in IDC may significantly reduce the incidence of VA,[20,21] more recently concern was expressed about the influence of antiarrhythmic agents on cardiac mortality.[22,23] However, in this series we found no relation between antiarrhythmic treatment and prognosis.

VA during effort in IDC have not been systematically investigated. In the report by Haissaguerre et al,[11] 28% of 113 patients developed VA during exercise stress testing; however a correlation with Holter monitoring findings was possible only in a minority of their cases. VA occurred in the present series in 37% of 168 cases during exercise testing, and were significantly more frequent and severe in patients with high-grade or repetitive forms documented at Holter monitoring; this finding suggests a heightened susceptibility to increased adrenergic tone at least in this subset of patients and supports the concept of electrical instability as a characteristic of IDC.

The relation between severity of VA and degree of ventricular dysfunction remains controversial. The present series encompasses the entire clinical and functional spectrum of IDC; in fact, left ventricular ejection fraction ranged from 8 to 52%. No index of left ventricular dimension and function correlated at either univariate or linear regression analysis to severity of VA; functional capacity at exercise stress testing was also similar in the 3 groups with different VA severity. When patients were stratified according to severity of ventricular dysfunction, distribution of VA over a wide range of left ventricular ejection fraction appeared to exclude a clear-cut correlation with the degree of ventricular dysfunction. Thus, VA may be considered a hallmark of IDC, independent of the clinical stage and the degree of pump function impairment.

Factors underlying the occurrence of VA in this disease can only be hypothesized and are beyond the scope of this study. Histomorphologic changes of the myocardium with disruption of cell-to-cell connection secondary to myofibrillar damage and fibrotic replacement have been well documented in most of these patients,[24,25] and may provide the anatomic substrate for altered conduction and automaticity. Furthermore, abnormalities of adrenergic nerve endings, which have been demonstrated by both histology[26] and radionuclide

imaging,[27] may create a local catecholamine imbalance. Electrolyte depletion, activation of neurohormonal mechanisms, and drug therapy may directly contribute to arrhythmogenesis.[22]

The prognosis of IDC has generally been considered poor[1–3]; however, in the 1980s, increased medical attention to the problem, and the introduction of new pharmacologic agents and tailored medical treatment of congestive heart failure have improved the life expectancy of patients with IDC and led to a substantial reduction in mortality rates even in very advanced cases.[4,5] In our series, 27 patients (13%) died from cardiac events, whereas 12 died suddenly. The low cardiac mortality observed may partially be explained by the fact that 59% of our patients were mildly symptomatic (New York Heart Association class I to II), whereas 45% had moderate ventricular dysfunction (defined as left ventricular ejection fraction >30 and <55%). However, this distribution probably better represents the spectrum of IDC observed at present in nontransplant centers, as a consequence of increased attention to the disease and earlier diagnosis.

Although there is general agreement regarding the prognostic relevance of pump dysfunction in IDC patients, conflicting data on VA as determinants of prognosis in IDC have been reported. The present study confirmed the prominent predictive value of ventricular impairment, but also found (in agreement with previous reports)[7,10,12,13] a significant association between VA and global cardiac mortality. We were unable to verify the correlation reported by other investigators[3,8,14] between prevalence and severity of VA, and incidence of sudden death, because of the low rate of sudden death in our series.

Holter monitoring in this study provided important prognostic information: in fact, severity of VA was a major independent determinant of cardiac death in 2 different multivariate models, immediately after an index of left ventricular dysfunction. Furthermore, patients with a higher VA grade had a higher 3-year mortality.

Severity of VA appeared more important in predicting prognosis than did the absolute number of any 1 form of VA; in fact, the numbers of ventricular premature complexes, pairs and tachycardia were not significantly related to outcome by either univariate or multivariate analysis.

APPENDIX

Italian Multicenter Cardiomyopathy Study (SPIC): *Participating centers:* Dipartimento di Cardiologia "A. De Gasperis," Ospedale Niguarda Cà Granda, Milan, Italy: Carlo Belli, MD, Claudio De Vita, MD, Maurizio Ferratini, MD, Fabio Recalcati, MD, Rita Vecchi, MD, and Edgardo Bonacina, MD; Servizio di Cardiologia San Luca, Ospedale Careggi, Florence, Italy: Alberto Dolara, MD, Franco Cecchi, MD, Mauro Ciaccheri, MD, Gabriele Castelli, MD, Vito Troiani, MD, Franca Gori, MD, and Maurizio Nannini, MD; Divisione di Cardiologia, Ospedale San Carlo, Milan, Italy: Franco Casazza, MD, Angela Capozzi, MD, and Roberto Mattioli, MD; Divisione di Cardiologia, Ospedale San Gerardo, Monza, Italy: Francesco Valagussa, MD, and Alessandro Bozzano, MD; Istituto di Fisiologia Clinica del C.N.R. di Pisa, Italy: Andrea Biagini, MD, Dianora Levorato, MD, Fabio Vernazza, MD, and Gualtiero Pelosi, MD; Divisione di Cardiologia, IRCCS Policlinico San Matteo, Pavia, Italy: Antonello Gavazzi, MD, Carlo Campana, MD, Gabriella Graziano, MD, Umbertina Veritti, MD, Eloisa Arbustini, MD, and Carlo Montemartini, MD; Divisione di Cardiologia, Ospedali Riuniti, Trieste, Italy: Fulvio Camerini, MD, Rossana Bussani, MD, Andrea Di Lenarda, MD, Gerardina Lardieri, MD, Luisa Mestroni, MD, Daniela Miani, MD, Alessandro Salvi, MD, Furio Silvestri, MD, and Gianfranco Sinagra, MD; Divisione di Cardiologia, Ospedale Civile, Rho, Italy: Laura Preti, MD, and Francesco Ferrari, MD; Divisione di Cardiologia, Ospedale di Circolo, Varese, Italy: Giovanni Binaghi, MD, and Marcalla Luvini, MD; Divisione di Medicina, Ospedale Bassini, Cinisello Balsamo, Italy: Romola Rumolo, MD, Luigi Carini, MD, Sergio De Ceglia, MD, and Elena Montani, MD; Servizio di Cardiologia, Consorzio Provinciale Antitubercolare, Milan, Italy: Aldo Sachero, MD, Erminia Giagnoni, MD, and Luigi De Cristofaro, MD; Ia Divisione di Medicina, Ospedale Monaldi, Naples, Italy: Massimo Cafiero, MD, Massimo Borgia, MD, Franco Costantino, MD, Attilio De Santis, MD, and Raffaele D'Oriano, MD; Divisione di Cardiologia, Ospedale Civile, Vicenza, Italy: Mario Vincenzi, MD, Maurizio Sartori, MD, and Renato Ometto, MD; Divisione di Cardiologia, Presidio Ospedaliero Multizonale, Treviso, Italy: Vincenzo Cuzzato, MD, Giuliano Renosto, MD, and Agnese Moro, MD.

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Prevalence and Etiology of Idiopathic Dilated Cardiomyopathy (Summary of a National Heart, Lung, and Blood Institute Workshop)

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Idiopathic dilated cardiomyopathy (IDC) is the primary indication for cardiac transplantation, with associated costs of approximately $177 million per year. Recognizing the economic implications of IDC, the increasing incidence, and the limited information on pathogenesis and prognosis, the National Heart, Lung, and Blood Institute convened a workshop on the Prevalence and Etiology of Idiopathic Dilated Cardiomyopathy on June 13 to 14, 1991. The difficulties of studying the disease were reviewed, including its relatively low prevalence, its potentially pluricausal nature, and the fact that it is often a diagnosis of exclusion. Still, it presents significant challenges to the cardiovascular scientific community, since the mechanism of myocardial damage and related etiologic and prognostic factors are virtually unknown. The development of more reliable measures of immune-mediated damage and noninvasive measures of impaired cardiac function present new research opportunities in this disorder.

Standardized diagnostic criteria for use in observational and interventional trials were developed, and priorities for future research were proposed. Population-based registries and nested case-control studies, where feasible, are appropriate study designs for tracking incidence and prevalence, and for identifying risk factors, respectively. Interventional studies should focus on secondary prevention, through modifying immune-mediated damage in clinically evident dilated cardiomyopathy, and through prevention of sudden death in patients with the disorder. Primary prevention trials must await the identification of modifiable risk factors and of appropriate and effective interventions.

(Am J Cardiol 1992;69:1458–1466)

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Idiopathic dilated cardiomyopathy (IDC) is an often fatal cause of heart failure characterized by ventricular dilatation and impaired systolic function. Reported mortality rates from cardiomyopathy have increased substantially since 1970, and currently over 10,000 deaths are attributed to cardiomyopathy in the United States annually.[1] Prevalence and incidence of the disorder also appear to be increasing,[2] although this may be due to improved case ascertainment. Few population-based estimates are available, and few geographic areas are represented in previous publications.

IDC is the primary indication for cardiac transplantation, with associated costs of approximately $177 million per year.[3] Costs associated with diagnosis and treatment of congestive heart failure secondary to IDC are likely several-fold higher. Recognizing the economic implications of IDC, the possibility of increasing incidence, and the lack of information on pathogenesis and prognosis, the National Heart, Lung, and Blood Institute convened a workshop on the Prevalence and Etiology of Idiopathic Dilated Cardiomyopathy on June 13 to 14, 1991. Objectives of the workshop, and of this report summarizing it, are: (1) to review existing information on IDC regarding incidence, prevalence, etiology, prognosis and treatment; (2) to formulate standard criteria for classifying IDC and subclinical cardiac impairment in population-based studies; and (3) to identify research priorities related to the etiology, prevention and treatment of IDC.

Characteristics of idiopathic dilated cardiomyopathy: CLINICAL PRESENTATION: Dilated cardiomyopathy is characterized by cardiac dilatation and systolic dysfunction. The condition was described by the World Health Organization as dilatation of the left, right or both ventricles, often severe, with impaired systolic function and invariably accompanied by hypertrophy. As part of the World Health Organization definition,[4] heart muscle disease of known cause or associated with disorders such as systemic or pulmonary hypertension, coronary artery disease, valvular heart disease or congenital cardiac anomalies should be excluded. Signs and symptoms include those of biventricular heart failure and low output states.

The commonly accepted criteria for left ventricular dilation include a cardiothoracic ratio >0.50 to 0.55 or a left ventricular internal diastolic dimension >2.7 cm/m^2 of body surface area. The common criteria for impaired systolic function include a depressed ejection fraction (<40 to 45%).

HISTOPATHOLOGIC FINDINGS: Microscopic features of IDC include substantial myocyte hypertrophy with

large, irregularly shaped, hyperchromatic nuclei.[5] Myofibrillar loss is evident, with sparse lymphocytic infiltrates and normal-appearing small vessels. Ultrastructurally, myocyte hypertrophy, myofibrillar loss, increased numbers of mitochondria, and mitochondrial changes are observed. Fibrosis is generally fine and perimyocytic, but may be coarse or more global, and is not characteristically found in watershed areas, as is ischemic fibrosis. "Ghost cells," or myocytes without myofibrillary elements, are typical, and the frequency of these empty cells is directly correlated with the degree of cardiac dilation and the severity of symptoms.

Subtypes of cardiomyopathy are difficult to separate morphologically. Although specific causes are difficult to distinguish, and findings in the idiopathic variety may be nonspecific, this should not imply that pathologic changes in IDC are absent. On the contrary, a completely normal biopsy does not support the diagnosis of IDC.

Diagnostic methods: Methods for diagnosis of IDC vary in invasiveness and accuracy (Figure 1). Minimally invasive tests such as gated radionuclide scanning are generally accepted as being more accurate than echocardiography in determining ejection fraction. However, echocardiography is readily available and noninvasive, and has the advantage of providing measures of wall thickness, chamber dimension, valvular disease and intracavitary thrombus. Right-sided cardiac catheterization can be used to quantify the characteristically elevated left ventricular filling pressures and to determine cardiac output. Left-sided cardiac catheterization can document elevated left ventricular end-diastolic pressure and diminished ejection fraction, as well as demonstrating the absence of coronary artery disease.

Endomyocardial biopsy can be performed to detect myocarditis and systemic infiltrative diseases, but findings are relatively nonspecific in the idiopathic variety. The overall use of endomyocardial biopsy in the context of dilated cardiomyopathy remains controversial. Approximately 12% of patients presenting within 6 months of onset of congestive heart failure with left ventricular dilation or dysfunction will have myocarditis on biopsy,[6] and biopsy is the only reliable technique for making this diagnosis. Biopsy is also useful in confirming adriamycin cardiotoxicity and in detecting infiltrative disorders. Although strong evidence of these latter can sometimes be obtained through other means, the diagnosis of infiltrative disorders can be missed by other organ biopsy specimens or overlooked by clinicians unfamiliar with the modes of presentation.

Endomyocardial biopsy may also become of greater use in the future as newer diagnostic techniques are used, such as polymerase chain reaction and in situ hybridization to evaluate infectious etiologies, or genetic analysis to evaluate specific cellular abnormalities. However, the diagnostic yield for myocarditis is relatively low given current routine histologic analysis, and the therapeutic implications of a positive biopsy are uncertain.

ECHOCARDIOGRAPHY: Echocardiography is gaining wider application in screening and follow-up of patients with dilated cardiomyopathy, primarily because of its noninvasive nature. Echocardiographic features include left ventricular dilation with normal or thin walls and diffuse hypokinesia.[7] Intracavitary thrombi are often present, most often in the left ventricular apex, and mitral and tricuspid regurgitation may be evident. End-diastolic volume >80 ml/m^2 is generally accepted as ventricular dilatation, and volumes may exceed 200 ml/m^2.[7] In 5 to 10% of patients dilation may be minimal or absent, but diffuse hypokinesia is demonstrable by radionuclide scanning in all.[8] Segmental wall motion abnormalities may be noted as well, and have been associated with a better prognosis.[9] Mitral E-point septal separation is another useful indicator of left ventricular dilation that is not dependent on left ventricular shape or symmetry. Mitral E-point septal separation >1 cm is considered to indicate left ventricular dysfunction, and >2 cm has been shown to correlate with an ejection fraction of <30%.[10] Differential diagnosis by echocardiography is difficult, but the technique is useful in ruling out primary valvular abnormalities.

Echocardiographic factors related to prognosis include end-systolic relative wall thickness, with thinner walls being associated with poorer prognosis.[7] Altered left ventricular shape, with a shift from an ellipsoidal to a spherical shape, is also a poor prognostic indicator,[11] as is abnormal transmitral filling measured by pulsed Doppler.[12] Asymptomatic or less symptomatic patients tend to have patterns of low early peak flow velocities and high late flows consistent with abnormal diastolic relaxation; symptomatic patients have the reverse pattern.

GALLIUM SCANNING AND ANTIMYOSIN ANTIBODY SCANNING: Two relatively new noninvasive techniques, gallium scanning and antimyosin antibody scanning, have

	Invasiveness				Accuracy			
	Low			High	Low			High
physical examination	X					X		
echocardiogram	X						X	
chest roentgenogram		X			X			
gated radionuclide scan			X				X	
right-sided heart catherization				X				X
left-sided heart catherization				X				X

FIGURE 1. Invasiveness versus accuracy of diagnostic techniques for idiopathic dilated cardiomyopathy.

TABLE I Survival in Established Dilated Cardiomyopathy

Investigators	No. of Pts.	Exclusion of Subjects with CAD	Survival at: 1 Year	2 Years	3 Years
Feild[15]	36	Excluded	69	50	33
Fuster[16]	104	Excluded	69	54	49
Franciosa[17]	182	Not excluded	66	41	24
ischemic	95	—	54	31	
IDC	87	—	77	52	
Unverferth[18]	69	Excluded	65		
Cohn[19]*	642	Not excluded		66	53
CONSENSUS[20]*	253	Not excluded	48		
Diaz[21]	169	Excluded	72	59	51
Roberts[22]	152	Excluded	75	59	48
Cohn[23]	139	Not excluded	76	54	41
Keogh[24]	79	Excluded	75	59	
Keogh[25]	232	Not excluded	68	56	41
Total (mean)	2,057		67	58	46

*Placebo group only.
CAD = coronary artery disease.

been used to detect acute myocardial inflammation. Resolution of uptake of gallium-67 citrate, which is concentrated at sites of inflammation, after treatment with prednisone and azathioprine has been associated with improved left ventricular function and decreased mortality in a small series,[13] suggesting that this technique may help identify patients likely to respond to immunosuppressive therapy.

Indium-111 antimyosin imaging also appears to be a useful indicator of both active myocarditis and prognosis. Normal myosin scans in a series of 82 patients were associated with a low rate of myocarditis detected by biopsy.[14] Patients with abnormal scans were 3 times as likely to have improvement in left ventricular function after immunosuppressive therapy, suggesting a role for this technique as a prognostic indicator.

Natural history and prognosis: Survival in patients with dilated cardiomyopathy is poor (Table I). Early studies showed little temporal improvement in survival.[15,16,21] More recent observations improved survival, but these findings could be explained by earlier diagnosis or better treatment.[26]

Factors associated with a more favorable prognosis include mild functional class, young age, female sex, and certain etiologies including peripartum and myocarditis. Ejection fraction is the most powerful predictor of mortality. [7] Poorer prognosis is also associated with presence of an S_3 gallop on examination, left bundle branch block on electrocardiogram, and enlarged cardiothoracic ratio on chest x-ray. Other poor prognostic factors include decreased wall thickness (<0.9 cm), decreased mass/volume ratio, pulmonary arterial wedge pressure or left ventricular end-diastolic pressure >20 cm, cardiac index <2.5 liters/min/m^2, and increased plasma levels of norepinephrine, atrial natriuretic factor and renin activity. Endomyocardial biopsy features associated with poor prognosis include increased cell size and fibrosis. Unfortunately, clinical assessment of prognosis in individual patients is difficult; patients rejected for transplantation as being "too healthy" have been demonstrated to have very poor survival despite absence of symptoms.[27]

Several etiologic types of dilated cardiomyopathy may be completely or partially reversible, including those due to alcohol, cobalt toxicity, acute myocarditis, peripartum myocarditis, septic shock, and cardiomyopathy due to uncontrolled tachycardia. Metabolic causes can also be completely reversible, including pheochromocytoma, thyroid disorders, hypocalcemia, hypophosphatemia and selenium deficiency.

Treatment: In the early stages of IDC, medical therapy of symptomatic congestive heart failure is the primary method of treatment. If that fails to control symptoms, transplantation supported by medical treatment is the mainstay of therapy. Multiple hospitalizations, either for management of worsening failure without transplantation, or for rejection and infections after transplantation, make costs of managing these patients quite high. These high costs, combined with unavailability of donor hearts, underscore the importance of developing strategies for primary prevention.

TRANSPLANTATION: Cardiac transplantation as a mode of treatment for IDC is changing, primarily because of increased competition for donor hearts. Between 1987 and 1990 the proportion of transplants performed for ischemic heart disease at Stanford increased dramatically, from 29 to 43% in the past year. In addition, costs of cardiac transplantation have been reimbursed by Medicare since 1986. The combined effect of these factors is that patients currently referred for transplantation are more likely to be older and to have ischemic disease. Given that the number of transplantations is limited by the availability of donors, there may be increased competition for and decreased availability of donor hearts for patients with IDC.

Patients undergoing transplantation for IDC do not appear to differ from patients with coronary artery disease in their risk of developing subsequent coronary disease in the graft, nor in their risk of developing rejection or infection[28] (and R. Vagelos, personal communication). Patients with ischemic heart disease have been reported to have higher mortality after transplantation than those with IDC,[29,30] although this has not been a universal finding[28] (and R. Bourge, personal communication).

There appears to be an increased risk of death secondary to rejection in blacks compared with whites, similar to the experience in renal transplantation.[31] Blacks are also more likely to develop progressive nephropathy after cyclosporine administration.[32] There is an urgent need to develop strategies for risk stratification before transplantation, and to identify those at high risk of death early after transplantation, and to identify those who will do well with or without transplantation.

MEDICAL THERAPY: The administration of β blockers shows some promise for those who can tolerate it,[33] and is currently being evaluated in a multicenter trial.[34] Metoprolol administration has been reported to reduce left ventricular ejection fraction, end-diastolic dimension, end-diastolic pressure, pulmonary arterial wedge pressure and systemic vascular resistance, while increasing systolic blood pressure, cardiac index and left ventricular stroke work index.[35] Withdrawal of metoprolol in this small series was followed by increases in heart rate

and left atrial dimension and decreases in ejection fraction, which reverted when the drug was readministered. Similar findings have been reported for bucindolol[36] and labetalol.[37]

Certain vasodilators have been shown to be effective in patients with congestive heart failure, with a reduction in 3-year mortality of 36%. Conventional therapy of congestive heart failure, including sodium restriction, diuretic drugs and digitalis glycosides, often provides considerable symptomatic relief. Enalapril has recently been demonstrated to reduce mortality in congestive heart failure in 2 large-scale clinical trials.[38,39]

Prednisone has been shown to increase ejection fraction modestly and transiently in patients with cardiomyopathy accompanied by lymphocytic or fibroblastic infiltration on biopsy examination, deposition of complement or immunoglobulins, or positive gallium scan, although improvements had reversed at the end of 1 year.[40] Prognostic factors included New York Heart Association functional class, right atrial pressure, pulmonary capillary wedge pressure, and left ventricular stroke work index.[41]

Epidemiology: INCIDENCE AND PREVALENCE: Few true incidence studies of IDC are available, and estimates vary considerably based on the diagnostic criteria employed. In western Denmark, an annual incidence of 5.4/100,000 cases was reported using clinical criteria and an additional 2.0/100,000 cases were detected at autopsy.[42] Annual incidence of dilated cardiomyopathy in Malmo, Sweden, was estimated at 7.5/100,000 cases,[43] and in 2 regions of England to be 8.3/100,000 population.[44] The age-adjusted incidence rate in Olmsted County, Minnesota, was estimated to be 6.0/100,000 person-years.[2] Of concern, this study documented an increased incidence with time (doubling from 3.9/100,000 in 1975 to 1979 to 7.9/100,000 in 1980 to 1984), although this may be due to improved case ascertainment. The age- and sex-adjusted prevalence of dilated cardiomyopathy in Olmsted County, Minnesota, as of January 1, 1985, was 36.5/100,000.[2]

Death certificate data from the National Center for Health Statistics[1] suggest a 2.5-fold increased risk in blacks than in whites, with black men having the highest prevalence (27/100,000 black men vs 11/100,000 white men). A case-control study from Baltimore also demonstrated a 2.7-fold increased risk of IDC associated with black race, which was not explained by differences in income, alcohol intake, body size, or other confounders.[45] No information is available about risk in Hispanic or Asian populations.

Diagnostic criteria have substantial effects on incidence and prevalence estimates, especially regarding the degree of rigor with which other causes of cardiomyopathy are excluded. In industrialized countries, the most likely competing diagnosis is ischemic left ventricular dysfunction, but in China selenium deficiency should be excluded, in Central and South Africa hypertension should be excluded, and in Central and South America Chagas' disease should be excluded.

ETIOLOGY AND RISK FACTORS: The determinants of IDC are poorly understood. Incidence appears to increase with age, and to be higher in men and in blacks.[1,45] Suggested etiologies include viral myocarditis and autoimmune or hyperimmune disorders. Known etiologies of (nonidiopathic) dilated cardiopathy include metabolic diseases (especially thyroid disorders and pheochromocytoma), toxic insults (alcohol, anthracyclines, lithium, cocaine), infiltrative diseases (such as hemochromatosis), genetic disorders, and increased sympathetic stimulation. Possible risk factor associations have been reported with diabetes, asthma, atopic diseases, hypertension, obesity, cigarette smoking and moderate alcohol consumption.[45,46]

RELATIONSHIP TO VIRAL MYOCARDITIS: IDC is believed frequently to be a sequela of viral myocarditis, and the distinction between the 2 conditions is often obscured in clinical studies. In the absence of biopsy-proved myocarditis, clinical evidence at the time of presentation is often inadequate to classify etiology as other than idiopathic.

Myocarditis is a histopathologic diagnosis based on presence of inflammatory infiltrates and myocardial cell necrosis. Care must be taken not to label as myocarditis any biopsy specimen with lymphocytes; myocarditis should not be diagnosed in the absence of myocyte damage. The high prevalence (87%) of infiltrates in end-stage cardiomyopathy and the variably stringent criteria with which the diagnosis of myocarditis is made may explain some of the variability in reported prevalence of myocarditis.[47]

Incidence of biopsy-proved myocarditis varies among reported series, from a low of 1 to 2% to a high of 67%.[14] The time from the onset of illness to the time of biopsy is related to the incidence of biopsy-proved myocarditis; in 1 series, 89% of biopsy samples were positive for myocarditis in 0 to 4 weeks, 70% in 4 to 12 weeks, and 38% in 12 to 26 weeks from the onset of symptoms.[48]

Correlation between the degree of left ventricular dysfunction and pathologic findings of myocarditis is poor, especially regarding the diffuseness, severity, and extent of infiltration and fibrosis.[49] This lack of correlation suggests the presence of an immune-mediated functional disorder or a circulating myocardial depressant that acts independently of direct structural damage. One such depressant may be tumor necrosis factor, which is elevated in congestive heart failure, and has been reported to have a myocardial depressant effect.[50,51]

IMMUNE ABNORMALITIES: Immune-mediated damage has received increased attention as a possible etiologic factor in the development of IDC, especially after acute myocarditis. An enteroviral genome can be demonstrated in 24% of patients with suspected myocarditis, in 37% of those with new-onset of IDC, in 29% of those with end-stage IDC, and in 2% of patients with ischemic left ventricular dysfunction.[52,53] Detection of enteroviral genomic material thus suggests that an active viral process may be ongoing with resultant myocarditis, or that left ventricular dysfunction may be a result of an immune response to viral infection. Abnormal major histocompatibility antigens may be detectable on myocytes in active myocarditis.[54] Putative autoantigens include adenine nucleotide translocator, branched-chain

ketoacid decarboxylase, β-adrenergic receptor, and cardiac myosin heavy chain.[55-57]

FAMILIAL CARDIOMYOPATHY: Some familial clustering of cardiomyopathy cases has been reported, and familial disease may be more frequent than is often appreciated.[58] Difficulties in confirming reports of affected family members and the presence of asymptomatic disease in family members appear to be obstacles in estimating the true prevalence of familial cases. Although dilated cardiomyopathy occurs more often in men, men less frequently had family histories of the disease (4% compared with 12% of women).[59] Recent studies have demonstrated that 20% of patients with idiopathic cardiomyopathy have at least 1 first-degree relative with a decreased ejection fraction and cardiac enlargement.[60] Approximately 6% of relatives of patients with IDC had left ventricular ejection fractions <50%.[60] In addition, slightly increased left ventricular dimension in systole or diastole, or both, occur in 13% of relatives, compared with an expected prevalence of 2%. Except for family history, no clinical or histopathologic characteristics have been detected that routinely distinguish familial from nonfamilial disease; familial disease may have the nonspecific pathologic findings of dilated cardiomyopathy or signs of myocarditis.[61] The mode of inheritance in most families appears to be autosomal dominant,[60] but the disease is genetically heterogeneous, with reports of autosomal recessive, X-linked recessive, and mitochondrial inheritance in individual families.

Specific etiologies of dilated cardiomyopathy: Because dilated cardiomyopathy is the end-stage of a variety of insults to the myocardium, and because mechanisms of cardiac damage in the idiopathic variety may be similar to those in other specific etiologies, the characteristics of several specific types of cardiomyopathy are reviewed briefly. This information may be useful in identifying factors related to prognosis of IDC and in designing intervention strategies for patients with IDC.

ALCOHOL: Alcoholic cardiomyopathy may hold important lessons for the study of IDC, particularly in that: (1) alcohol use is widespread and may exacerbate other myocardial insults, (2) subclinical cardiac abnormalities are detectable in alcoholics long before signs and symptoms of impaired cardiac function appear, and (3) the disorder appears to be reversible by abstinence until very late in its course.[62] Factors associated with increased risk of alcoholic cardiomyopathy are primarily the quantity, frequency and duration of alcohol use, but also include poor nutrition, heavy metal contamination of beverages (especially cobalt and lead), male gender, cigarette use and age at onset.[63] A subclinical form of the disorder, characterized primarily by left ventricular enlargement, has been identified in up to 45% of alcoholic patients.[64]

ANTHRACYCLINE: Anthracycline cardiomyopathy is similar in many respects to other toxic cardiomyopathies. Adriamycin cardiomyopathy is dose-related, with a threshold phenomenon at a cumulative dose of 450 to 550 g/m^2.[65] This threshold suggests that some type of reserve must be exhausted before the myopathy is expressed. Other risk factors include extremes of age, preexisting coronary disease, hypertension, malignant myocardial or pericardial involvement, prior irradiation, and co-existent chemotherapy with alkylating agents.[66] Incidence appears to have declined recently due to increasing use of continuous infusion rather than bolus therapy and to a reduction in dose in many chemotherapeutic protocols.

Long-term sequelae of adriamycin use include abnormal diastolic function and increased wall stress.[67] Echocardiography in children a median of 6 years after treatment shows increased wall stress and decreased thickness, without the expected increase in wall thickness associated with growth.[68] This suggests that anthracyclines may have a persistent effect in inhibiting the synthesis of cardiac muscle proteins to prevent normal growth.

Abnormalities of cardiac function are detectable after even minimal doses of anthracyclines, suggesting that prevalence is largely dependent on the measurement technique. Biopsy findings generally precede functional derangement,[69] and severity of abnormalities progresses fairly uniformly with increasing dose.[70] Reversibility of cardiac dysfunction, even in severe cases, has been reported but is unusual.[71]

SELENIUM DEFICIENCY: Cardiomyopathy associated with selenium deficiency (Keshan's disease) has characteristic pathologic findings that include large, swollen myocytes that progress to dense fibrotic scarring.[72] The disorder is distributed geographically in areas with low selenium in the soil and the disease can be prevented or reversed by treatment with sodium selenite.[73] Selenium deficiency is rare in the United States but has been reported in patients receiving total parenteral nutrition.[74] Keshan's disease is thought to be completely reversible with treatment.

INFECTIOUS CARDIOMYOPATHY: Dilated cardiomyopathy can be a sequela of a variety of infections, but is most often ascribed to trypanosomiasis and viral myocarditis. Trypanosomiasis is intriguing because there can often be a long delay between the childhood acute infection and the cardiomyopathy, which may not become fully manifest until the fourth to sixth decade. Viral myocarditis progressing to cardiomyopathy is thought to be due most frequently to Coxsackie virus, but estimates of incidence and prevalence are difficult to obtain because the disease is so often asymptomatic. Risk factors include male gender, malnutrition, pregnancy, ischemia, immune suppression, medications and extremes of age.[75] Recently, cardiomyopathy associated with the acquired immunodeficiency syndrome has been described as a discrete clinical entity characterized by heart failure, ventricular dysfunction and ventricular arrhythmias.[76]

PERIPARTUM CARDIOMYOPATHY: Peripartum cardiomyopathy is frequently defined as the development of left ventricular dilatation and systolic dysfunction in the last month of pregnancy or 5 months postpartum, in the absence of a definable etiology or demonstrable heart disease during pregnancy.[77] In a series from Loyola University, 43% of patients with peripartum cardiomyopathy developed the disorder in their last trimester, 34% within 1 week of delivery, the remainder between 2 and 12 weeks of delivery, and none beyond 12 weeks.[78]

Improvement appears to occur early (within 6 weeks) or not at all. Rapidity of improvement has a significant bearing on prognosis.

An immunologic mechanism has been suggested for the disease because immunologic function is known to be altered during pregnancy, with suppressor T-cell function rising shortly postpartum.[79,80] In addition, myocarditis has been demonstrated on biopsy in 30% of peripartum patients, compared with an average of 9% in idiopathic nonperipartum cases.[78] Finally, cardiac rejection appears to recur more frequently in patients with peripartum cardiomyopathy (50 to 88%) (M.R. Costanzo-Nordin, personal communication).

Recommended criteria for classifying idiopathic dilated cardiomyopathy and subclinical cardiac impairment in population-based studies: The World Health Organization definition,[4] although valid and useful, may be incomplete for the purpose of epidemiologic studies. Criteria based on noninvasive measurements should be included where feasible. Exclusions should be carefully defined and adjusted to the specific research questions to be pursued, as too strict an interpretation of exclusion criteria may limit the scope and value of epidemiologic surveys of dilated cardiomyopathy. When exclusion criteria are used, their definitions should be explicitly stated.

Definition of idiopathic dilated cardiomyopathy for epidemiologic surveys: 1. Ejection fraction by echocardiography, radionuclide scanning or ventriculography <45% or M-mode fractional shortening <30%, or both, in the presence of an end-diastolic left ventricular diameter >2.7 cm/m^2.

2. EXCLUSIONS: (1) significant coronary artery disease, including prior myocardial infarction, angina, or >50% obstruction in a major coronary vessel with accompanying myocardial dysfunction; (2) active myocarditis (endomyocardial biopsy may be necessary); (3) metabolic diseases; (4) significant, persistent, untreated hypertension; and (5) isolated right ventricular dilated cardiomyopathy (including arrhythmogenic right ventricular dysplasia).

Exclusion of patients with demonstrable coronary artery disease may produce bias in some studies, since most older adults in developed countries have some degree of coronary disease. There is little evidence to suggest that idiopathic cardiomyopathy cannot occur in the presence of mild to moderate atherosclerosis. Excluding all patients with any coronary disease may therefore produce a biased and poorly generalizable sample. Conversely, including such patients in a study of IDC may contaminate outcome with a second disease, particularly since patients with ischemic left ventricular dysfunction appear to have a worse prognosis than those with idiopathic disease. A reasonable compromise may be to include patients with coronary disease defined by angiography as a separate and well-defined subgroup, with specific hypotheses to be addressed.

3. SEPARATE CATEGORIES (TO BE INCLUDED BUT CLEARLY DISTINGUISHED): (1) alcohol abuse (one definition might be >5 drinks/day or 100 g of alcohol/day and continued use during prior 12 months); and (2) peripartum cardiomyopathy.

TABLE II Possible Etiologic Factors in IDC

Nonmodifiable factors
Age
Sex
Race or ethnicity
Genetic predisposition
Asthma or atopic diseases
Modifiable factors
Viruses
Enteroviruses
HIV
Influenza
Diet
Alcohol
Selenium
Socioeconomic status
Metabolic conditions
Drugs
Cocaine
Bronchodilators
Sympathomimetics
Cytotoxic agents
Toxic or occupational exposures
Cobalt
Lead
Cadmium
Smoking
Obesity
Hypertension

IDC = idiopathic dilated cardiomyopathy; HIV = human immunodeficiency virus.

Definition of idiopathic dilated cardiomyopathy for interventional studies: Diagnostic criteria and exclusions are the same as those for epidemiologic studies, with the following additions: (1) Coronary angiography should be mandatory in subjects at risk of significant coronary disease. (2) Endomyocardial biopsy is strongly recommended to rule out specific heart muscle disease, and especially to rule out active myocarditis.

Definition of subclinical cardiac impairment: Diagnostic criteria and exclusions are the same as those for epidemiologic studies of IDC, with the following subclassifications: (1) asymptomatic IDC — left ventricular dilation and systolic dysfunction without symptoms; and (2) subclinical cardiac impairment — left ventricular dilation and systolic dysfunction without symptoms or signs on physical examination.

The earliest stages of IDC may be characterized by cardiac dilation without detectable dysfunction in the resting state. Stress testing with exercise, persantine, adenosine or vasoconstrictors may be helpful in unmasking occult coronary disease or latent abnormalities of left ventricular function.

Research priorities related to idiopathic dilated cardiomyopathy: OBSERVATIONAL STUDIES: Observational studies of IDC should address the variety of possible etiologic factors discussed in this workshop (Table II). Specific measurements that should be considered are listed in Table III. A basic science approach, emphasizing investigation of biochemical and immunologic abnormalities or of possible candidate genes, e.g., should be incorporated into any such studies. Immunologic and neurohumoral factors may be altered by the onset and progression of the disease.

TABLE III Measurements to be Included in Population-Based Studies of IDC

DNA polymorphisms and candidate genes
Cardiac structure defined by echocardiogram
Immunologic markers
HLA typing
Cytotoxic antibodies
Suppressor T-cell function
Cytotoxic killer cells
Neurohumoral factors
Norepinephrine levels
Atrial natriuretic factor
Renin
Endothelin

DNA = deoxyribonucleic acid; HLA = human leukocyte antigen; IDC = idiopathic dilated cardiomyopathy.

The echocardiogram is recommended as the principal method of detection, diagnosis and follow-up for population-based studies. For serial studies employing echocardiography, indexes of preload and afterload such as heart rate, blood pressure, and assessment of volume status must be recorded and kept as constant as possible.

Etiologic study designs for IDC were prioritized as follows:

1. *Population-based registries:* Such registries should be referable to a large, defined population and heterogeneous as to age, gender, race, and socioeconomic status. Examples might include the Armed Forces, large health maintenance organizations, and other defined sources of health care.

2. *Prospective studies of unaffected persons:* Given the low incidence and prevalence of IDC, prospective studies of general populations are feasible only if data have already been collected in very large numbers. Nested case-control studies would be a more cost-effective alternative, if previously collected data could be obtained from serum banks, health maintenance organization, or other sources. Follow-up of high-risk groups such as family members or alcoholic patients might permit smaller prospective studies to be performed in selected populations.

3. *Registries not based on populations:* Case registries could be based in referral hospitals or on identified candidates for transplantation or clinical trials. Such registries could be used for family studies, for estimates of prevalences of risk factors compared with normal populations, and for identification of etiologic and prognostic subsets.

4. *Case-control studies:* Although prone to numerous biases, properly performed case-control studies are the most efficient manner of studying a variety of risk factors in rare diseases. Care should be taken to distinguish factors that are affected by the presence of disease.

Interventional studies: Workshop participants concluded that current information on etiology and course of IDC is sufficient to justify the development of treatment trials. As in all clinical trials, interventions should have clear potential for improving the course of the disease and a definite rationale for their use, and information on safety must be available. Candidate interventions include:

1. *Immunosuppression:* Current data support ongoing immune-mediated damage as an important mechanism for progressive failure in IDC, and one that may be amenable to treatment. Modification of ongoing immune-mediated damage after acute (if unrecognized) viremia should be the focus of interventional efforts. Patients should be randomized to receive immunosuppression versus placebo, with all patients receiving conventional therapy. Care should be taken to distinguish end points clearly, with mortality being the primary end point, followed by ventricular function, and then by other carefully selected functional measures. Children should also be included, since they represent a substantial proportion of potentially postviral cardiomyopathies.

2. *Beta blockers:* As a second possibility for interventional study, β blockade may be useful in subsets of patients with IDC. Care must be taken to demonstrate tolerance to the agents before randomization. While this intervention may only be useful in selected groups, it may be promising, and subsets could possibly be identified and followed using autoantibodies to β receptors.

3. *Prevention studies:* Current evidence is insufficient to propose preventive trials at this time, since effective preventive efforts (other than avoidance of cardiotoxins) are currently unknown. More data on factors associated with development and progression of IDC are needed from observational studies before specific preventive measures can be investigated.

Once preventive interventions are identified, prevention studies should focus on groups at high risk, such as family members of presumed familial cases, patients with asthma, patients receiving anthracyclines, and alcoholic or peripartum patients at risk.

4. *Sudden cardiac death:* Interventions should be developed to prevent sudden cardiac death in patients with IDC, since sudden death accounts for the majority of deaths in these patients.[81,82] Implantable or transvenous defibrillators may serve as a bridge to transplantation in this group, since many patients die suddenly while awaiting a transplant. However, it is not clear that trials of implantable defibrillators in patients specifically with IDC are needed, or whether results from trials in broader groups of patients might be applicable to patients with IDC.

Summary of recommendations: (1) Criteria for left ventricular dilation and impaired systolic function should be evaluated prospectively, by correlation with biopsy, other diagnostic criteria or prognosis. (2) Simple, inexpensive, noninvasive methods for detecting coronary artery disease are needed to rule out the disease in patients with suspected IDC; whereas such methods may not be accurate enough for planning surgical intervention, they would be quite useful in large-scale studies. (3) Information on risk stratification for transplant candidates is urgently needed, with a goal of identifying those at high risk of death after transplantation, and those who will do well without transplantation. (4) Population-based registries should be established to track

incidence and prevalence and to identify representative cases to study potential etiologic factors in case-control investigations. (5) Given the potentially pluricausal nature of the disorder, patients and control subjects selected for in-depth study should be characterized carefully to identify the probable extensive heterogeneity among patients that could mask important associations. (6) Immunologic markers appear to provide a link between myocarditis and IDC, and should be incorporated into studies of etiology and treatment. (7) Interventional studies should focus on modifying immune-mediated damage in clinically evident IDC and on prevention of sudden death. (8) Primary prevention trials must await the identification of modifiable risk factors and of appropriate and effective interventions.

APPENDIX

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Clinical Impact of Balloon Angioplasty for Branch Pulmonary Arterial Stenosis

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The clinical impact of percutaneous balloon angioplasty on the management of patients with native or postoperative pulmonary arterial stenosis was reviewed. Seventy-four patients underwent 110 angioplasty procedures. Mean age at dilation was 6.7 ± 5.3 years (range 0.2 to 18.1), 17 patients were aged <1 year, mean follow-up was 37.7 ± 22.8 months (range 16 to 96), and 34 patients (44%) had follow-up angiography. Pulmonary artery dilation was acutely successful in 53% of patients, 17% had recurrent stenosis, and 5% had complications. The impact on subsequent care was favorably influenced in 26 of 74 patients (35%) with either complete resolution of stenosis (n = 7), optimizing future surgical conditions (n = 14), reduction in right ventricular pressure by >20% (n = 3), or improvement of ipsilateral lung perfusion (n = 2). No patient previously considered inoperable was subsequently considered suitable for surgical repair owing to the intervention. No correlation was found between success and cardiac diagnosis (p = 0.48), site of stenosis (p = 0.78), balloon–vessel ratio (p = 0.42), or whether the stenotic area consisted of native or synthetic material (p = 0.22). No predictive factors for success could be defined, and often there was only a transient clinical impact. Due to the low complication risk and potential for a beneficial result, it still appears prudent to offer angioplasty as an initial therapeutic modality in this setting.

(Am J Cardiol 1992;69:1467–1470)

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Balloon dilation techniques have become an integral component in the treatment of a variety of congenital heart lesions including pulmonary[1,2] and aortic valve stenoses,[3] and recurrent coarctation of the aorta.[4,5] Because direct surgical approaches to pulmonary artery hypoplasia and stenosis have generally been disappointing, several investigators have used percutaneous balloon angioplasty techniques in this setting to relieve the hemodynamic burdens imparted by the stenotic vessels.[6–8] Rothman et al[9] recently reported from a large series a 58% acute success rate for such procedures, with a 16% incidence of recurrent stenosis and minimal complications. The clinical impact of this interventional procedure on the subsequent care of these patients (i.e., whether an advantageous outcome has resulted) has not been examined in detail. Thus, we reviewed the results of 110 pulmonary artery angioplasties in 74 patients over a 7-year period to determine the impact that dilation had on subsequent management, and the presence or absence of any predictors to aid in optimal patient selection.

METHODS

Study patients and diagnosis: The hemodynamic data, angiograms, lung perfusion scans and medical records of 74 patients (40 male and 34 female) who underwent pulmonary artery balloon dilation between July 1984 and January 1991 were reviewed. Mean age at dilation was 6.7 ± 5.3 years (range 0.2 to 18.1), with 17 patients dilated at <1 year of age, and in all, 110 stenotic vessels dilated. Patient diagnoses are listed in Table I; postoperative pulmonary atresia (34%), tetralogy of Fallot (18%) and truncus arteriosus (14%) were the most frequent cardiac lesions.

Indications for pulmonary artery dilation included: (1) systemic right ventricular pressures; (2) marked decrease in flow to the ipsilateral lung determined by angiography or lung perfusion scanning; (3) documented stenosis in the distal pulmonary vascular tree considered not easily accessible by a surgical approach, or as a prelude to definitive surgical repair of the underlying lesion, or both; (4) discrete proximal branch artery stenosis; and (5) symptomatology of increasing hemoglobin concentration or cyanosis with evidence of stenosis considered amenable to balloon therapy.

Technique: All procedures were performed after informed parental consent was obtained, and the protocol was approved by the human subjects protection committee. Procedures were performed using general anesthesia and standard hemodynamics, and selective angiography was performed. Balloon catheter diameters were initially chosen to be 3.5 to 4[6,8] times the stenotic

TABLE I Cardiac Diagnosis

	No.	Outcome: Acute +	Acute −	Follow-Up +	Follow-Up −
Postoperatively obtained					
Pulmonary atresia—VSD, RV-PA	25	13	12	8	17
Conduit	10	7	3	5	5
Truncus arteriosus, RV-PA conduit	13	7	6	4	9
Tetralogy of Fallot	8	4	4	2	6
Postarterial repair TGA	4	3	1	1	3
Double-outlet right ventricle	2	2	0	2	0
Aortopulmonary septal defect, VSD	5	2	3	2	3
Isolated					
Proximal branch PA stenosis	4	2	2	2	2
Peripheral branch PA stenosis	3	0	3	0	3
		p = 0.48		p = 0.48	

PA = pulmonary artery; RV = right ventricle; TGA = transposition of great arteries; VSD = ventricular septal defect; + = successful; − = unsuccessful.

TABLE II Stenosis Location

	No.	Outcome: Acute +	Acute −	Follow-Up +	Follow-Up −
Proximal branch pulmonary artery	80	42	38	41	40
Site of aortopulmonary shunt	8	4	4	4	4
Distal to aortopulmonary shunt	13	7	6	7	6
Distal pulmonary artery–isolated	9	4	5	4	5
		p = 0.97		p = 0.95	

+ = successful; − = unsuccessful.

TABLE III Vessel Constituent at Site of Stenosis

	No.	Outcome: Acute +	Acute −	Final +	Final −
Polystan	12	4	8	3	9
Dacron	8	2	6	2	6
Gore-tex	8	3	5	3	5
Native vessel	51	27	24	21	30
Homograft	20	13	7	13	7
Pericardium	11	6	5	4	7
		p = 0.33		p = 0.22	

+ = successful; − = unsuccessful.

vessel diameter, with inflation times of up to 20 to 45 seconds. Balloon sizes were increased until a waist appeared and could not be eliminated, using maximally rated balloon inflation pressures (usually 3 to 5 atm) monitored by an in-line manometer. High-pressure rated balloons (10 to 12 atm) were not generally used. Repeat inflation–deflation cycles (up to 10 to 20) were performed until the waist disappeared or it was clear that no further enlargement was possible. Postprocedure angiography was performed in all patients. Pre- and postprocedure lung perfusion scans were also obtained (n = 40) to assess the proportion of pulmonary blood flow to each lung.

Success criteria: Acute success was judged using the criteria of Rothman et al[9] (i.e., >50% increase in vessel diameter, >20% increase in flow to the dilated lung, or 20% decrease in right ventricular–systemic pressure ratio). Clinical success was arbitrarily defined as follows: (1) clinical improvement resulting in postponing anticipated surgery on the pulmonary artery; (2) improvement in vessel diameter, which makes a previously considered inoperable patient, operable; (3) optimizing the surgical procedure by: (a) allowing delay in surgery to allow patient growth, (b) allowing growth of the affected vessel, or (c) normalization of right ventricular pressure; or (4) sustained improvement of dilated vessel diameter (as defined previously) documented at subsequent angiography or lung perfusion scans. Fulfillment of any 1 criterion was considered adequate for the procedure to be classified as a clinical success.

Statistical analysis: An unpaired *t* or rank-sum Wilcoxon test was used for intergroup comparisons of continuous variables, and the paired *t* or sign-rank Wilcoxon test was used for intergroup comparisons. Results are expressed as mean ± SD. Analysis of group comparisons used a chi-square contingency analysis for categoric variables. A p value <0.05 was chosen to indicate significance.

RESULTS

Acute outcome: The 74 patients in this cohort underwent a total of 110 pulmonary artery dilations. One catheterization procedure was performed in 58 patients, 2 procedures in 13, and 3 procedures in 3. One artery was dilated in 40 patients, 2 arteries in 25, 3 arteries in 4, and 4 arteries in 2. The mean increases in right and left pulmonary artery diameters were 4.3 ± 2.1 to 6.7 ± 2.5 mm, and 5.4 ± 2.7 to 6.3 ± 2.5 mm (p <0.01), respectively. Combining criteria for acute success, 53% (58 of 110) of dilations were successful. Of these successful dilations, 55 were the result of an increase in vessel diameter, 2 were due to a reduction in right ventricular-to-systemic pressure ratio, and 1 was due to improved lung perfusion. Of the 40 patients with pre- and postperfusion lung scans, only 2 achieved the success criteria. Excluding patients with ventricular septal defects, only 14 demonstrated a reduction in right ventricular/systemic pressure ratio, and concurrent increases in pulmonary artery diameters. In 5 patients, the pulmonary artery was dilated through a modified Blalock-Taussig shunt, and all 5 had successful technical procedures, with an acute success rate of 40% (2 of 5). No difficulty in passing the balloon catheter down the graft was encountered, and serial dilations with increasing balloon diameters were possible. The mean balloon-to-stenosis diameter ratio was 3.5 (range 1.5 to 7.5). No relation was found between balloon size and vessel diameter ratio, and success or failure (success 3.6 ± 1.1 and failure 3.4 ± 1.1, p = 0.42). Similarly, no correlation was found between acute success, failure and location of stenosis (p = 0.97) (Table II). Likewise, when comparing acute success rate with the constituents of the vessel being dilated (Table III), no correlations were observed (p = 0.33).

Clinical outcome: Mean follow up was 38 ± 29 months (range 6 to 96). Forty patients underwent subsequent surgical intervention (16 before a second angiogram was performed). Time to surgery was 7 ± 6 months (range 1 to 29). Thirty-four patients (44%) underwent a second angiographic study 18 ± 13 months (range 3 to 48) after the initial procedure, which documented recurrent stenosis in the dilated vessel in 17% (6 of 34). Pulmonary artery angioplasty had an advantageous influence on clinical management in 35% (26 of 74) of patients. In 7 patients, resolution of stenosis resulted in avoidance of any further intervention, and further surgery was technically simplified in 11 and could be delayed in 4. Right ventricular pressures decreased >20% in 3 patients, and an improvement in lung perfusion scan was seen in 2. No correlations were found when comparing outcome with location of stenosis ($p = 0.78$), or vessel material dilated ($p = 0.22$).

Complications: Six angioplasty procedures (5%) were associated with complications. There were no related patient deaths or symptomatic femoral vein thromboses. In 1 patient after a wire perforation of the left pulmonary artery associated with pulmonary hemorrhage, subsequent angiography documented a large 2 × 2 cm saccular aneurysm that was successfully coil-occluded before surgical repair of the associated cardiac lesion 8 months later. No other patient developed pulmonary edema or hemorrhage. A saccular aneurysm (defined as dilation >2 times the adjacent artery diameter, with abrupt tapering) was seen in 4 patients; all 4 cases were associated with stenosis of small vessels distal to systemic-to-pulmonary arterial shunts. Follow-up angiography in 2 patients revealed no change in the size of the vessels. No relation to patient age, weight, balloon-to-vessel diameter ratio and development of such aneurysms was found. One patient developed ventricular fibrillation due to catheter manipulation; the procedure was abandoned after successful defibrillation, and the child subsequently underwent elective surgical repair.

DISCUSSION

This is the first study to examine the clinical impact of pulmonary artery angioplasty on the pediatric age group, previous studies concentrating on initial success rates, complications and technical issues.[6–8] In this regard, Rothman et al[9] reported an acute success rate of 58% (127 of 218 dilations), with recurrence in 16%, and complications in 6%. In the present study, a success rate of 53% (with recurrence in 17%, and complications in 5%) suggests that patient selection and the techniques used were similar. However, clinical management was favorably influenced by the procedure in only 35% of patients, whereas in most cases there was only marginal or no influence on the subsequent clinical care. Furthermore, no patient in whom pulmonary anatomy contributed to inoperability was subsequently considered suitable for surgical repair as a result of the procedure. However, there was a major apparent benefit from sequential dilations resulting in transient clinical improvement that allowed postponement of a surgical procedure. Contrary to previous studies,[6,8,9] a more successful outcome for acquired (postsurgical) compared with native stenosis was not observed in this study. In patients with pulmonary atresia, multiple peripheral artery dilations at 1 procedure were performed to manage diffuse peripheral arterial disease characteristic of that lesion. However, the effects were considered beneficial by the aforementioned criteria in only 8 of 25 patients. In the transposition postarterial repair group, 7 patients had branch pulmonary arterial stenosis after a LeCompte maneuver[10] (2 of whom also had discrete supravalvar pulmonary stenosis), and 1 had stenosis of left and right patch angioplasty sites. All patients with stenoses secondary to the LeCompte maneuver had an unsuccessful result, with the vessels expanding fully on inflation, but recoiling after balloon deflation. Likewise, dilation of the supravalvar stenoses had no effect on outflow gradients. The only patient to respond in this group had stenosis secondary to a patch angioplasty. These observations concur with those of Sexena et al,[11] noting the effects of dilation (improved vessel diameters and lower right ventricular pressures) as transient (returning to predilation levels within 3 months).

In contrast to other reports,[6,8,9] no relation between balloon size–vessel diameter ratio and acute outcome was found. The reason for this is unclear, although balloon–vessel ratios of <2 were found in a number of very small peripheral stenoses owing to technical limitations set by the diminutive distal vessel. However, successful acute outcomes were inevitably associated with obliteration of the stenotic balloon waist during inflation. Furthermore, no association between age or weight and outcome was observed.

Despite improvement in vessel diameter in 51% of dilations, only 2 patients had an increase in lung perfusion of >20% from that at baseline. The influence of multiple stenoses and peripheral arterial disease with regional inhomogeneity of flow adversely affects the interpretation of such scans as an indicator of success. However, regional improvements in perfusion may result from specific vessel dilation, resulting in some patients having clinical improvement in the absence of an improved scan.[12]

Complications: Complications occurred in 5% of procedures, which is comparable with previous reports.[9] The saccular lesions seen in 4 patients were similar to those previously reported,[9] and no balloon–vessel ratio was found to be predictive. Angiographic follow-up in 2 patients demonstrated no change in vessel size, and in all, there have been no complications due to this vessel distortion. The only large aneurysm was caused by a guidewire perforation and was successfully coil-occluded before further intracardiac surgery.

Study limitations: Several limitations are inherent to this study. By design, the study was retrospective, and dilation techniques and balloon technology developed over time, with several operators performing procedures. The use of so-called high-pressure balloons that can withstand higher intraballoon pressures than those used in this study may allow obliteration of the stenotic waist in some cases that were found to be nondilatable. Clinical outcome was classified according to an arbitrarily defined set of criteria, incorporating clinical, sur-

gical and angiographic factors. The surgical criteria of "optimizing the surgical procedure" was subjective, based on each surgeon's unique view of how the angioplasty impacted the surgical approach. Furthermore, the overall success rate for the cohort is at worst optimistic in that "success" was granted to a patient if any 1 of the aforementioned criteria was satisfied. An attempt to determine the probability of a particular variable being predictive of success or failure by multivariant analysis was precluded owing to the small number of patients.

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Outcome of Prenatally Detected Cardiac Malformations

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Reliable, prenatal detection of congenital heart disease has become possible over the past decade with the evolution of fetal echocardiography. We have documented the outcome of 170 cardiac defects diagnosed prenatally since 1984. Of 170 cases, 55 (32%) had major extracardiac malformations and 45 (28%) chromosomal abnormalities (16 had both). Elective termination was chosen in 77 (45%) pregnancies. Of 93 continuing pregnancies 15 were stillborn and 43 died postnatally (48% of these fetuses and infants had extracardiac or chromosomal anomalies, or both). Thirty-five patients survive at 1 to 80 months (mean 36). Aneuploidy or extracardiac defects are present in 20% of survivors. Nonimmune hydrops secondary to cardiac failure was present in 7 continuing pregnancies and none of these patients survived. The prognosis of prenatally diagnosed cardiac lesions is negatively influenced by the presence of cardiac failure, aneuploidy or extracardiac malformations, or a combination of these. Optimal counseling and management requires the identification of these conditions when present.

(Am J Cardiol 1992;69:1471–1474)

During the past decade the fetal echocardiogram has become a standard procedure for assessing the fetus identified to be at risk for congenital heart disease.[1–3] The reliability and accuracy of this procedure has been confirmed.[4,5] It has been suggested that prenatal detection of cardiac malformations not only aids in parental counseling, but also ensures optimal care for the infant at, and following, delivery.[6,7] However, the reported survival rate for continuing pregnancies has been discouragingly low (21%).[8] This study examines the impact of prenatal diagnosis of cardiac anomalies over a 7-year period in our center, which has been actively performing fetal cardiac scans since 1977. Patients seen before 1984 were excluded from the study because this period was considered investigational.

METHODS

Between March 1984 and March 1991, 3,016 patients underwent fetal echocardiograms. Indications for referral were known risk factors for congenital heart disease (Table I).[9] The study results were reviewed and positive cases identified. The outcome of each pregnancy complicated by fetal heart disease was documented after examining the hospital records of mothers and live-born infants followed at the Yale–New Haven Hospital and by contacting the referring physicians of those cases followed elsewhere.

Fetal echocardiographic studies were performed between 16 and 39 weeks gestation using 3.5 or 5.0 mHZ transducers (Hewlett-Packard model 77020 AC Andover, Massachusetts; Advanced Technology Laboratories, UltraMark 9, Bothell, Washington). Four-chamber, long-axis, short-axis and arch (ductal and aortic) 2-dimensional views were obtained. Pulsed and color flow Doppler interrogation were performed once this technology became available. All studies were videotaped and available for review.

All patients also underwent a targeted, general fetal scan for anomalies at the same visit, providing documentation of extracardiac malformations. Results of chromosomal evaluations on samples obtained by amniocentesis, fetal blood sampling or postmortem examination were recorded when available.

At initial diagnosis patients were informed of the cardiac lesion and counseled regarding options for pre- and postnatal management. These included the option of termination in pregnancies encountered before 24 weeks gestation, and of delivery at a center with expertise in the management of congenital heart disease immediately available. The option of nonintervention with compassionate care of the infant postnatally was considered for those with severe cardiac lesions such as aortic atresia, or those with incapacitating extracardiac or chromosomal abnormalities.

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TABLE I Structural Congenital Heart Disease: Referral Indications for Fetal Echocardiograms and Relative Yield of Each

Indication	No. (%)	No. Positive	Relative Yield (%)
Family history	896 (30)	15	2
Arrhythmia	459 (15)	4	1
Extracardiac anomaly	451 (15)	49	1
Maternal diabetes	303 (10)	9	3
Teratogen exposure	258 (9)	3	1
Suspicious level I scan	150 (5)	57	38
Aneuploidy	130 (4)	17	13
Hydrops	61 (2)	14	23
Other	308 (10)	3	1

TABLE II Chromosome Disorders in 158 Patients, and Outcome

	Trisomy 21	Trisomy 18	Trisomy 13	XO	Other
Total	16	16	5	3	5
Termination	11	11	3	2	4
Intrauterine death		3		1	
Postnatal death	1	2	2		1
Alive	4				

XO = Turner syndrome.

TABLE III Major Extracardiac Malformations Diagnosed*

	Total	Termination	Intrauterine death	Postnatal death	Alive
Ventral wall defect	17 (2)	9	1	7	—
Neurologic	11 (5)	8		2	1
Duodenal atresia	6 (2)	2		4	
Cystic hygroma	6 (2)	2	2	1	1
Renal	3	3			
Conjoined twins	2	2			
Esophageal atresia	2 (1)	1	1		
Biliary atresia	1			1	
Multiple	7 (4)	2	2	3	

*Numbers in brackets are cases with coexistent chromosomal abnormality.

RESULTS

Of 3,016 fetal patients studied, 171 (5.7%) congenital cardiac malformations were identified (Table I). Whereas the majority of scans were indicated because of a family history of congenital heart disease (30%), fetal arrhythmia (15%) and extracardiac fetal anomaly (15%), the highest yields were from the groups referred with suspicious basic fetal scans (38%), nonimmune hydrops (23%), chromosomal abnormalities (13%) and extracardiac malformations (11%).

Follow-up data were obtained in 170 of the 171 cases. For the 170 lesions followed, elective termination was chosen in 77 (45%). The outcome of the 93 (55%) continuing pregnancies is seen in Figure 1. Fifteen went on to spontaneous intrauterine death and 78 infants were live-born. Thirty-five survive at 1 to 80 months (mean 36) follow-up. Most of the survivors (n = 30) have undergone at least 1 surgical intervention.

Chromosome analysis, available in 158 patients, was abnormal in 45 (28%) (Table II). Excluding patients referred with aneuploidy, chromosomes were abnormal in 28 cases (20%). There were 55 patients with major extracardiac malformations (16 with aneuploidy) (Table III). Chromosome results were obtained in 93 of 100 patients not referred with aneuploidy and in whom no extracardiac malformation was present, and were abnormal in 14 (15%).

Of the 77 terminated cases, 31 had abnormal chromosomes (11 with extracardiac malformations), and 18 had major extracardiac anomalies without documented aneuploidy. Thus, 64% of terminated fetuses had serious extracardiac disease. Another fetus with atrioventricular septal defect and Ellis-Van Creveld syndrome was also terminated. In fetuses with isolated cardiac disease who underwent termination, the lesions were uniformly severe, and at best a palliative procedure (e.g., Norwood procedure or transplant for aortic atresia) was the only surgical option (Table IV).

In the 93 continuing pregnancies, extracardiac and chromosomal abnormalities were seen in 21 (23%) and 14 (15%), respectively. Ten of the 15 fetuses in whom spontaneous intrauterine death (67%) occurred had either abnormal chromosomes (n = 4) or extracardiac malformations (n = 6). The remainder had aortic atresia (n = 2), aortic stenosis, cardiomyopathy or Ebstein's anomaly (1 each).

Of 78 live-born infants, 43 subsequently died. Thirty deaths were in patients in whom no intervention was undertaken because of either the severity of the lesion (n = 7), poor cardiac function with associated hydrops (n = 4), or the presence of incapacitating chromosomal (n = 5) or extracardiac malformations (n = 13). One newborn with complex transposition and limb anomalies also died after the parents had him discharged against

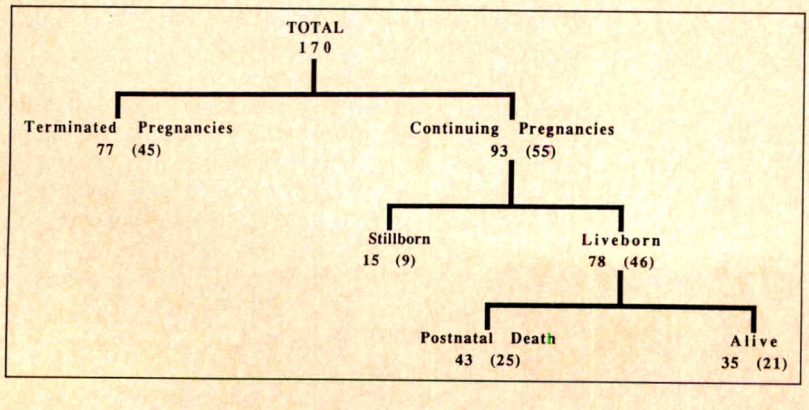


FIGURE 1. Outcome of 170 pregnancies with prenatally detected cardiac malformations. Numbers in *parentheses* are percentages.

TABLE IV Isolated Cardiac Malformations Electively Terminated (n = 27)

Cardiac Diagnosis	No.
Aortic valve atresia	8
Critical aortic stenosis	5
Univentricular connection	4
Atrioventricular septal defect*	2
Cardiomyopathy	2
Tricuspid atresia	2
Other†	4

*These 2 patients had nonimmune hydrops, which was associated with complete heart block in 1.
†One case each of critical pulmonary stenosis and nonimmune hydrops, Ebstein anomaly and pulmonary atresia, and 1 of transposition of the great arteries with hypoplastic left ventricle, pulmonary stenosis and common atrium.

medical advice. Of the remaining 48 patients, 43 underwent surgery and 30 survived.

The outcome of individual cardiac lesions is listed in Table V. The elective termination rate was highest for lesions frequently associated with aneuploidy (double-outlet right ventricle with trisomy 18, atrioventricular septal defect with trisomy 21) and for lesions in which palliation, rather than anatomic correction, was the only available treatment.

In continuing pregnancies the spontaneous fetal and infant mortality rates for aortic valve atresia (10 of 11) and critical aortic stenosis (6 of 6) are expectedly high. Ebstein's anomaly of the tricuspid valve accounted for 7 (4%) lesions, and the outcome was poor in all but 1 of 5 continuing pregnancies. There were 6 deaths in 15 live-born patients with atrioventricular septal defects including 2 with extracardiac malformations, 2 with postnatal development of severe subaortic stenosis, and 1 with nonimmune hydrops. Six patients with tetralogy of Fallot died including 2 with pentalogy of Cantrell, and 1 each with trisomy 18, trisomy 13 and microcephaly. The 3 patients with simple ventricular septal defect who succumbed had severe extracardiac anomalies. Three of 6 live-born infants with transposition of the great arteries were treated with compassionate care only due to extracardiac malformations in 2 and parental refusal of medical care in 1. Nonimmune hydrops secondary to cardiac failure was present in 7 continuing pregnancies and heralded prenatal or neonatal death in all instances. It contributed to the poor outcome in the 4 of 5 continuing pregnancies in which atrial isomerism was complicated by complete heart block.

When the first and last 3 years of the study were compared, no significant trends were observed.

DISCUSSION

The highest yield of cardiac malformations was seen in cases referred with suspicious 4-chamber views. This highlights the importance of obtaining a 4-chamber view in screening fetal ultrasound examinations.[10] The relatively high incidence of cardiac anomalies identified in referred cases with chromosome and extracardiac abnormalities also underscores the importance of echocardiographic screening in these instances.[11,12] One may have anticipated a higher percentage of cardiac anomalies among aneuploidic fetuses than the 13% incidence noted in this study; however, most of these referrals had

TABLE V Cardiac Diagnoses and Outcome

Cardiac Diagnosis	Total	Termination	Intrauterine Death	Postnatal death	Alive
Atrioventricular defect	37	20	2	6	9
Aortic valve atresia	22	11	4	6	1
Double-outlet right ventricle	15	10	2	3	
Ventricular septal defect	14	6	2	1	5
Tetralogy of Fallot	11	2		6	3
Critical aortic stenosis	11	5	1	5	
Univentricular connection	7	4		2	1
Ebstein's anomaly	7	2	1	3	1
Atrial isomerism	6	1		4	1
Transposition	6	1		2	3
Coarctation	5	1			4
Pulmonary atresia	5	2	1	2	
Pulmonary stenosis	4	1		1	2
Tricuspid atresia	4	4			
Truncus arteriosus	3			2	1
Atrial septal defect	2				2
Pulmonary atresia with ventricular septal defect	1				1
Other	10	7	2		1

only low level mosaicism (i.e., the majority of cells were eukaryotypic).

Chromosomal abnormalities or extracardiac malformations were present in 84 (49%) cases (16 cases [10%] had both). The 20% incidence of chromosomal abnormalities in patients referred without known aneuploidy exceeds the risk estimates of 5 to 12%, based on postnatal results, offered by other workers.[13–15] The discrepancies between the postnatal statistics, and these and other prenatal statistics, likely reflect the high prenatal loss of these fetuses.[11,16,17] We found a 15% incidence of aneuploidy in patients with isolated cardiac disease compared with a 28% incidence in those with extracardiac malformations.

The presence of noncardiac problems contributed to the decision to terminate in 49 of 77 cases (64%). In 93 continuing pregnancies these complicating factors were identified in 28 of 58 patients (48%) who died pre- or postnatally, and only in 7 of 35 (20%) long-term survivors (all survivors with aneuploidy have trisomy 21). This indicates a poorer outcome for patients with serious noncardiac disease ($p < 0.01$). These findings emphasize the need to obtain a genetic evaluation and a complete fetal survey so as to counsel parents effectively about patient viability and candidacy for surgery.

Some prenatally diagnosed cardiac lesions, even when isolated, are often incompatible with life.[18,19] Nonimmune hydrops is usually fatal when associated with structural cardiac malformations, as it was in our 7 cases.[8,20,21] The fatal outcome of all but 1 patient with severe aortic obstruction is similar to the experience of Sharland et al.[8] To a degree this may reflect our conservative approach to these lesions. Ebstein's anomaly and atrial isomerism accounted for a substantial number of fetal diagnoses (7 [4.1%] each), a frequency which exceeds that seen among the newborn population with congenital heart disease.[22] The higher incidence of severe, complex cardiac lesions diagnosed prenatally versus postnatally, reflects, in part, the increased likelihood

of identifying cardiac lesions that have altered 4-chamber anatomy and are thus more readily detectable on basic scans.[23]

In utero diagnosis provides the opportunity for altering perinatal management strategies.[3,7] Nonetheless, the survival rate of our study population was only 38% (35 of 93) of continuing pregnancies, including 15 stillbirths. Of the 43 deaths in 77 live-born infants, no intervention was provided in 30. Thus 13 live-born infants, despite aggressive therapy, died (1 secondary to noncardiac disease and 1 with nonimmune hydrops). These infants exhibited a variety of complex lesions. There was 1 case of tetralogy with absent ductus (the latter finding was not documented prenatally) in which the fetus had an ultimately fatal hypoxic insult following the expedient use of prostaglandin E_1 postnatally. This medication no doubt aggravated the right-to-left ventricular shunt and consequent hypoxia by decreasing the systemic vascular resistance. Thus, this case may in fact represent an example in which prospective care contributed to the poor outcome.

The 35 survivors displayed a broader spectrum of malformations for which 30 have required surgery to date. It is difficult to prove that the prenatal diagnosis favorably influenced the outcome of these patients, but survival occurred in all patients surgically treated for coarctation of the aorta and for transposition. Previous knowledge of the lesion may allow one to better avoid the consequences of ductal closure that impact negatively on these and other potentially ductal-dependent lesions. Twelve of our 35 survivors had ductal-dependent cardiac disease.

One more readily apparent benefit of prenatal diagnosis is that it allows the medical team to counsel parents prenatally. Diagnoses made before the legal limit for termination allow this choice to be opted for. In our population, in all cardiac lesions but 1, elective termination was undertaken only in the presence of major extracardiac or chromosomal abnormalities, or both, nonimmune hydrops, or if eventual biventricular repair was impossible. In continuing pregnancies, the in utero diagnosis gave parents time to assimilate the information without the urgency often required postnatally. This is especially valuable when the option of noninterventional postnatal care is offered, as in aortic atresia.

Sharland et al[8] also recently examined the outcome of patients with prenatally diagnosed cardiac anomalies. Differences between the 2 studies include a slightly better outcome (38 vs 21%) for continuing pregnancies in this study. However, it is difficult to compare the 2 reports, because the former did not present the cardiac diagnoses for terminated cases even though the lesion-specific termination rates may markedly affect the overall outcome for continuing pregnancies. Societal and cultural differences, both nationally and internationally, also influence decisions regarding termination and postnatal care, and thus affect survival rates.

In summary, a review of our most recent 7 years' experience demonstrated that nearly half of all prenatally diagnosed cases of structural heart disease were terminated, the majority of these being associated with chromosomal or extracardiac anomalies, or both. Among continuing pregnancies, the high frequency of severe, complex lesions contributed to a discouragingly high incidence of fetal and infant death. The high frequency of chromosomal and extracardiac abnormalities and in utero cardiac failure further contributed to fatality among continuing pregnancies. In fact, if we exclude patients who succumbed for these reasons, or were not considered surgical candidates because of their cardiac diagnosis, we are left with 46 live-born patients, of whom 35 survived.

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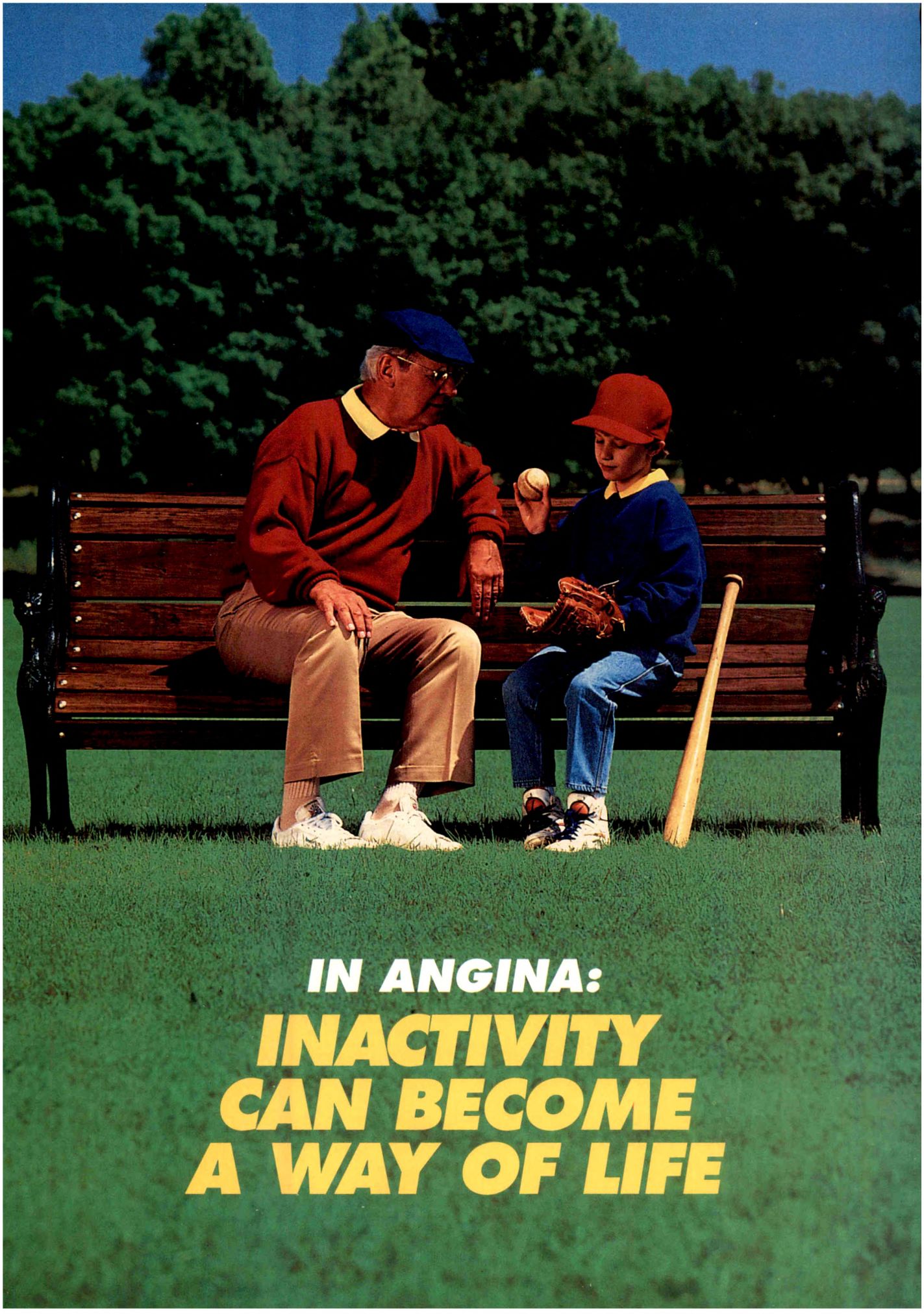
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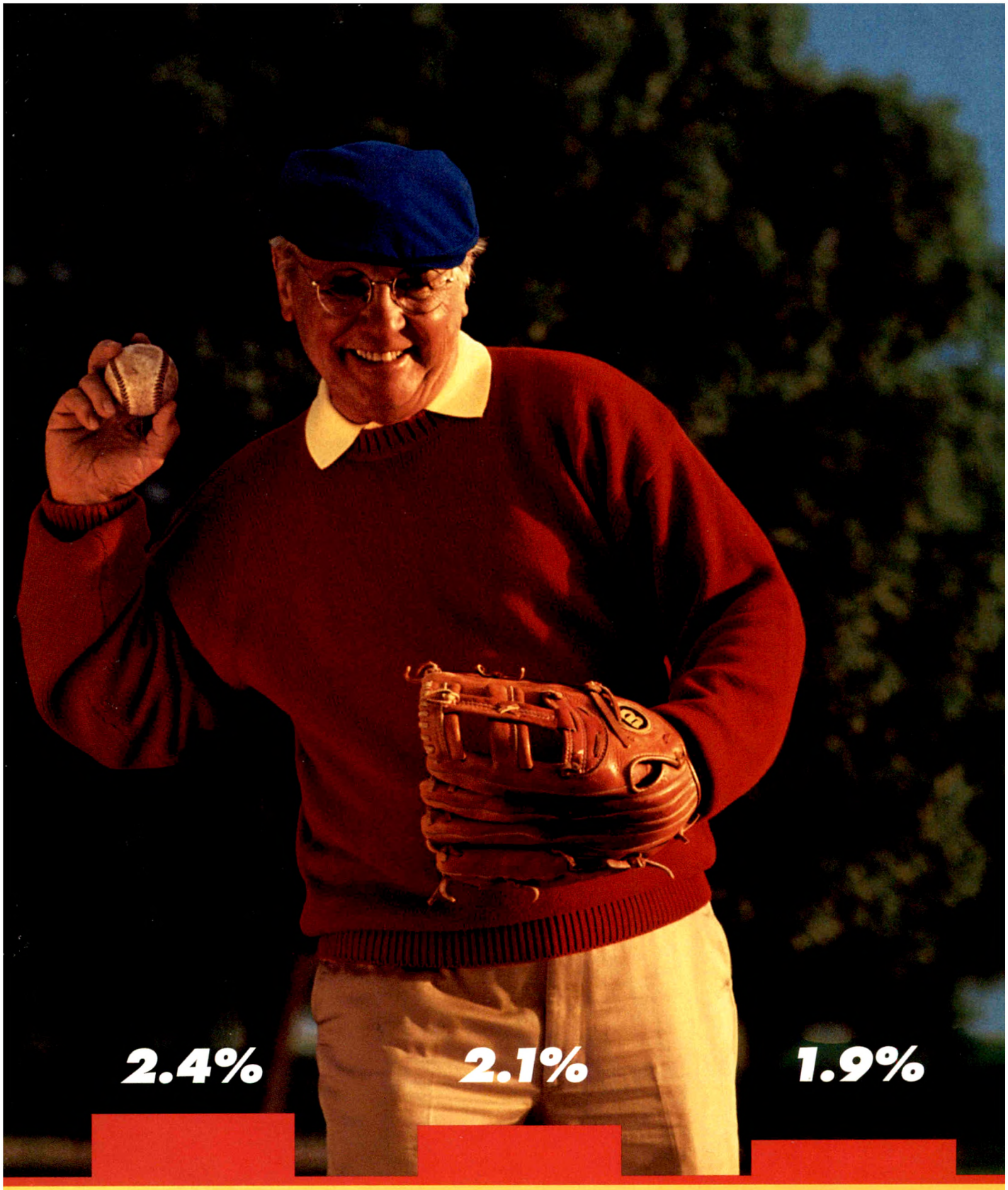
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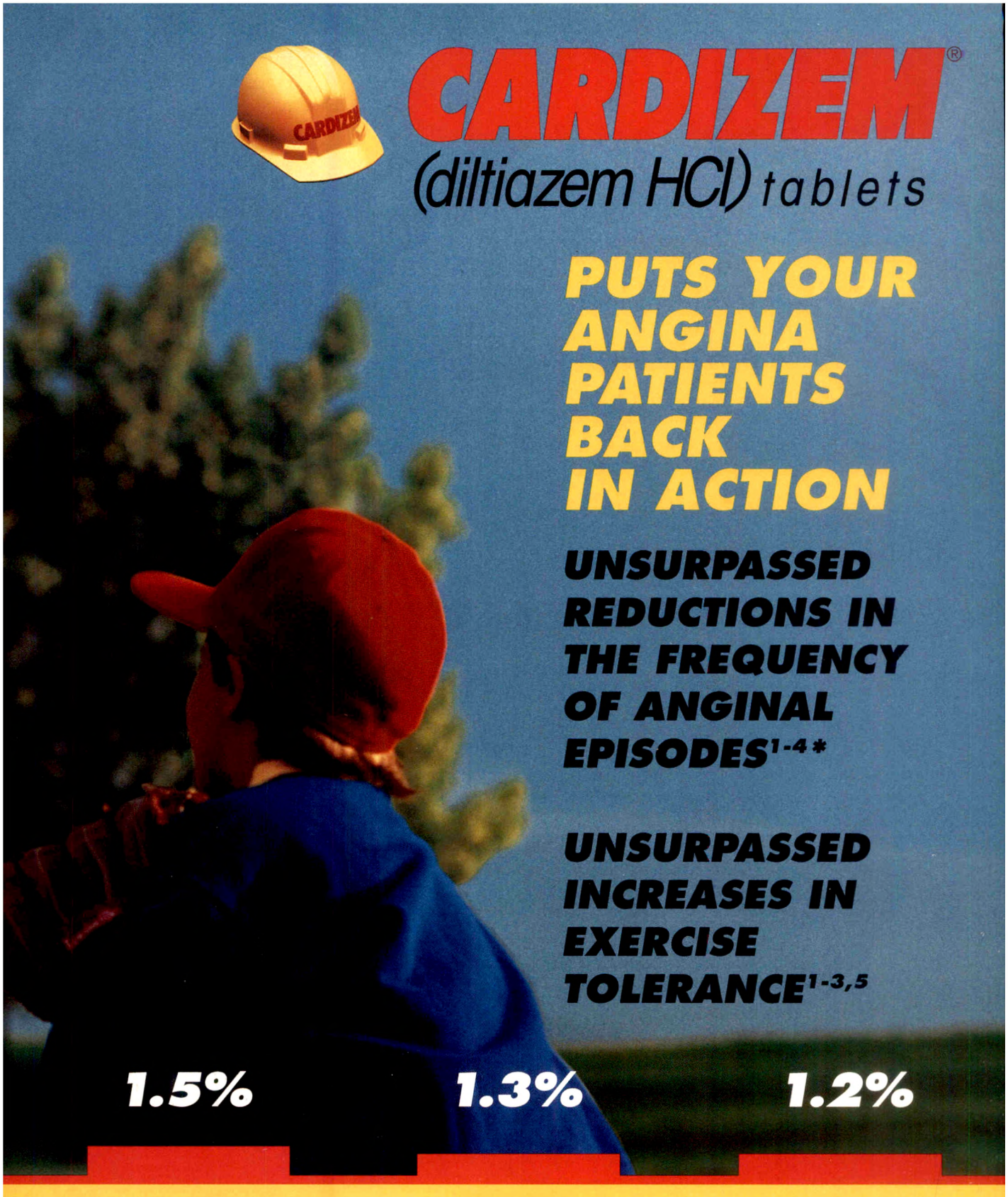

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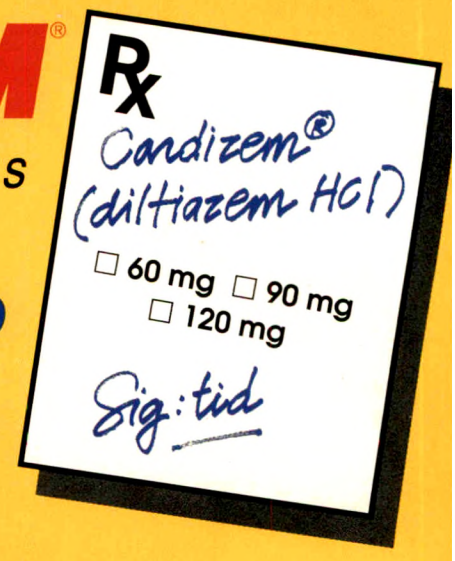
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BRIEF SUMMARY
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CONTRAINDICATIONS

CARDIZEM is contraindicated in (1) patients with sick sinus syndrome except in the presence of a functioning ventricular pacemaker, (2) patients with second- or third-degree AV block except in the presence of a functioning ventricular pacemaker, (3) patients with hypotension (less than 90 mm Hg systolic), (4) patients who have demonstrated hypersensitivity to the drug, and (5) patients with acute myocardial infarction and pulmonary congestion documented by x-ray on admission.

WARNINGS

1. **Cardiac Conduction.** CARDIZEM prolongs AV node refractory periods without significantly prolonging sinus node recovery time, except in patients with sick sinus syndrome. This effect may rarely result in abnormally slow heart rates (particularly in patients with sick sinus syndrome) or second- or third-degree AV block (six of 1,243 patients for 0.48%). Concomitant use of diltiazem with beta-blockers or digitalis may result in additive effects on cardiac conduction. A patient with Prinzmetal's angina developed periods of asystole (2 to 5 seconds) after a single dose of 60 mg of diltiazem.
2. **Congestive Heart Failure.** Although diltiazem has a negative inotropic effect in isolated animal tissue preparations, hemodynamic studies in humans with normal ventricular function have not shown a reduction in cardiac index nor consistent negative effects on contractility (dp/dt). Experience with the use of CARDIZEM alone or in combination with beta-blockers in patients with impaired ventricular function is very limited. Caution should be exercised when using the drug in such patients.
3. **Hypotension.** Decreases in blood pressure associated with CARDIZEM therapy may occasionally result in symptomatic hypotension.
4. **Acute Hepatic Injury.** In rare instances, significant elevations in enzymes such as alkaline phosphatase, LDH, SGOT, SGPT, and other phenomena consistent with acute hepatic injury have been noted. These reactions have been reversible upon discontinuation of drug therapy. The relationship to CARDIZEM is uncertain in most cases, but probable in some. (See PRECAUTIONS.)

PRECAUTIONS

General. CARDIZEM (diltiazem hydrochloride) is extensively metabolized by the liver and excreted by the kidneys and in bile. As with any drug given over prolonged periods, laboratory parameters should be monitored at regular intervals. The drug should be used with caution in patients with impaired renal or hepatic function. In subacute and chronic dog and rat studies designed to produce toxicity, high doses of diltiazem were associated with hepatic damage. In special subacute hepatic studies, oral doses of 125 mg/kg and higher in rats were associated with histological changes in the liver which were reversible when the drug was discontinued. In dogs, doses of 20 mg/kg were also associated with hepatic changes; however, these changes were reversible with continued dosing.

Dermatological events (see ADVERSE REACTIONS section) may be transient and may disappear despite continued use of CARDIZEM. However, skin eruptions progressing to erythema multiforme and/or exfoliative dermatitis have also been infrequently reported. Should a dermatologic reaction persist, the drug should be discontinued.

Drug Interaction. Due to the potential for additive effects, caution and careful titration are warranted in patients receiving CARDIZEM concomitantly with any agents known to affect cardiac contractility and/or conduction. (See WARNINGS.)

Pharmacologic studies indicate that there may be additive effects in prolonging AV conduction when using beta-blockers or digitalis concomitantly with CARDIZEM. (See WARNINGS.)

As with all drugs, care should be exercised when treating patients with multiple medications. CARDIZEM undergoes biotransformation by cytochrome P-450 mixed function oxidase. Coadministration of CARDIZEM with other agents which follow the same route of biotransformation may result in the competitive inhibition of metabolism. Dosages of similarly metabolized drugs, particularly those of low therapeutic ratio or in patients with renal and/or hepatic impairment, may require adjustment when starting or stopping concomitantly administered CARDIZEM to maintain optimum therapeutic blood levels.

Beta-blockers: Controlled and uncontrolled domestic studies suggest that concomitant use of CARDIZEM and beta-blockers or digitalis is usually well tolerated. Available data are not sufficient, however, to predict the effects of concomitant treatment, particularly in patients with left ventricular dysfunction or cardiac conduction abnormalities.

Administration of CARDIZEM (diltiazem hydrochloride) concomitantly with propranolol in five normal volunteers resulted in increased propranolol levels in all subjects and bioavailability of propranolol was increased approximately 50%. If combination therapy is initiated or withdrawn in conjunction with propranolol, an adjustment in the propranolol dose may be warranted. (See WARNINGS.)

Cimetidine: A study in six healthy volunteers has shown a significant increase in peak diltiazem plasma levels (58%) and area-under-the-curve (53%) after a 1-week course of cimetidine at 1,200 mg per day and diltiazem 60 mg per day. Ranitidine produced smaller, nonsignificant increases. The effect may be mediated by cimetidine's known inhibition of hepatic cytochrome P-450, the enzyme system probably responsible for the first-pass metabolism of diltiazem. Patients currently receiving diltiazem therapy should be carefully monitored for a change in pharmacological effect when initiating and discontinuing therapy with cimetidine. An adjustment in the diltiazem dose may be warranted.

Digitalis: Administration of CARDIZEM with digoxin in 24 healthy male subjects increased plasma digoxin concentrations approximately 20%. Another investigator found no increase in digoxin levels in 12 patients with coronary artery disease. Since there have been conflicting results regarding the effect of digoxin levels, it is recommended that digoxin levels be monitored when initiating, adjusting, and discontinuing CARDIZEM therapy to avoid possible over- or under-digitalization. (See WARNINGS.)

Anesthetics: The depression of cardiac contractility, conductivity, and automaticity as well as the vascular dilation associated with anesthetics may be potentiated by calcium channel blockers. When used concomitantly, anesthetics and calcium blockers should be titrated carefully.

Carcinogenesis, Mutagenesis, Impairment of Fertility. A 24-month study in rats and a 21-month study in mice showed no evidence of carcinogenicity. There was also no mutagenic response in in vitro bacterial tests. No intrinsic effect on fertility was observed in rats.

Pregnancy. Category C. Reproduction studies have been conducted in mice, rats, and rabbits. Administration of doses ranging from five to ten times greater (on a mg/kg basis) than the daily recommended therapeutic dose has resulted in embryo and fetal lethality. These doses, in some studies, have been reported to cause skeletal abnormalities. In the perinatal/postnatal studies, there was some reduction in early individual pup weights and survival rates. There was an increased incidence of stillbirths at doses of 20 times the human dose or greater.

There are no well-controlled studies in pregnant women; therefore, use CARDIZEM in pregnant women only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers. Diltiazem is excreted in human milk. One report suggests that concentrations in breast milk may approximate serum levels. If use of CARDIZEM is deemed essential, an alternative method of infant feeding should be instituted.

Pediatric Use. Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Serious adverse reactions have been rare in studies carried out to date, but it should be recognized that patients with impaired ventricular function and cardiac conduction abnormalities have usually been excluded.

In domestic placebo-controlled angina trials, the incidence of adverse reactions reported during CARDIZEM therapy was not greater than that reported during placebo therapy.

The following represent occurrences observed in clinical studies of angina patients. In many cases, the relationship to CARDIZEM has not been established. The most common occurrences from these studies, as well as their frequency of presentation, are: edema (2.4%), headache (2.1%), nausea (1.9%), dizziness (1.5%), rash (1.3%), asthenia (1.2%). In addition, the following events were reported infrequently (less than 1%):

Cardiovascular:	Angina, arrhythmia, AV block (first degree), AV block (second or third degree—see conduction warning), bradycardia, bundle branch block, congestive heart failure, ECG abnormality, flushing, hypotension, palpitations, syncope, tachycardia, ventricular extrasystoles.
Nervous System:	Abnormal dreams, amnesia, depression, gait abnormality, hallucinations, insomnia, nervousness, paresthesia, personality change, somnolence, tremor.
Gastrointestinal:	Anorexia, constipation, diarrhea, dysgeusia, dyspepsia, mild elevations of alkaline phosphatase, SGOT, SGPT, and LDH (see hepatic warnings), thirst, vomiting, weight increase.
Dermatological:	Petechiae, photosensitivity, pruritus, urticaria.
Other:	Amblyopia, CPK elevation, dry mouth, dyspnea, epistaxis, eye irritation, hyperglycemia, hyperuricemia, impotence, muscle cramps, nasal congestion, nocturia, osteoarticular pain, polyuria, sexual difficulties, tinnitus.

The following postmarketing events have been reported infrequently in patients receiving CARDIZEM: alopecia, erythema multiforme, extrapyramidal symptoms, gingival hyperplasia, hemolytic anemia, increased bleeding time, leukopenia, purpura, retinopathy, and thrombocytopenia. There have been observed cases of a generalized rash, characterized as leukocytoclastic vasculitis. In addition, events such as myocardial infarction have been observed which are not readily distinguishable from the natural history of the disease in these patients. A definitive cause and effect relationship between these events and CARDIZEM therapy cannot yet be established. Exfoliative dermatitis (proven by rechallenge) has also been reported.

HOW SUPPLIED

CARDIZEM® (diltiazem hydrochloride) is available in bottles of 90 (60 mg, 90 mg, 120 mg tablets), bottles of 100 (30 mg, 60 mg, 90 mg, 120 mg tablets), bottles of 500 (30 mg, 60 mg tablets), and UDIP® packages of 100.

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Cardiac Characteristics and Postoperative Courses in Cushing's Syndrome

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To assess the cardiac characteristics and postoperative courses in patients with Cushing's syndrome, electrocardiography and echocardiography were performed to study 12 consecutive, unselected patients, and results were compared with those of essential hypertension and primary aldosteronism. Eleven patients had hypertension and 7 had diabetes mellitus. Before adrenalectomy, common electrocardiographic abnormalities consisted of high-voltage QRS complexes (10 patients) and negative T waves (7 patients). Echocardiograms showed left ventricular hypertrophy in 9 patients, and all the patients had evidence of asymmetric septal hypertrophy. In patients with left ventricular hypertrophy, the thickness of the interventricular septum ranged from 16 to 32 mm, whereas the ratio of the thickness of interventricular septum to that of the posterior wall ranged from 1.33 to 2.67. The interventricular septum in Cushing's syndrome was extremely thicker and asymmetric septal hypertrophy occurred more often than essential hypertension and primary aldosteronism. Nine patients could be followed up after operation. In these patients abnormal electrocardiographic findings had normalized, the thickness of interventricular septum had decreased and asymmetric septal hypertrophy had disappeared except in 1 patient. The reason why left ventricular hypertrophy in Cushing's syndrome is severe is still unknown. Because left ventricular hypertrophy is more severe and the frequency of asymmetric septal hypertrophy much greater in Cushing's syndrome than in essential and other secondary hypertension, it is thought that not only increased aortic pressure but excessive plasma cortisol may be etiologic factors in the progression of left ventricular hypertrophy in Cushing's syndrome.

(Am J Cardiol 1992;69:1475–1480)

Cushing's syndrome develops when excess amounts of the adrenocortical hormones, especially cortisol, are secreted. It is characterized by truncal obesity, moon face, fatigability and weakness, amenorrhea, hirsutism, purplish abdominal striae, edema, osteoporosis, glycosuria and hypertension. This syndrome was first described by Harvey Cushing in 1932.[1] The etiology of this syndrome was adrenal hyperplasia due to adrenocorticotropic hormone–producing tumors of either the pituitary gland (Cushing's disease) or of nonendocrine tissue, adrenal adenomas, adrenal carcinomas and so on. Left ventricular hypertrophy is frequently seen in Cushing's syndrome and is thought to be due to hypertension. Of the 12 cases reported by Cushing in 1932, hypertension occurred in 9 and cardiac hypertrophy in 4 of the 8 autopsied cases. Sholz et al[2] reported that hypertension was found in all of their 17 cases and cardiac hypertrophy in 15 of 17 cases. Until now, however, there has been no detailed report on cardiac hypertrophy and its postoperative course in Cushing's syndrome. To ascertain the incidence and types of anatomic cardiac abnormalities in patients with Cushing's syndrome, we studied 12 consecutive patients with Cushing's syndrome with electrocardiograms and echocardiograms before elective surgery and followed up 9 after surgery.

METHODS

The study group comprised 12 consecutive patients with Cushing's syndrome hospitalized at our hospital between 1979 and 1990. Two patients had Cushing disease, 1 had an adrenal carcinoma and 9 had adrenal adenomas. There were 4 men and 8 women, aged from 27 to 57 years (Table I). All patients presented with typical clinical pictures of Cushing's syndrome with increased plasma cortisol and increased urinary 17-hydroxycorticosteroids. In all patients, the normal circadian rhythm in the levels of plasma cortisol and adrenocorticotropic hormone was absent. In 10 patients with adrenal adenoma or adrenal carcinoma elevated baseline levels of urinary 17-hydroxycorticosteroids could not be suppressed with administration of 2 and 8 mg of dexamethasone. Serum potassium was within normal limits in all patients. The urinary adrenaline, urinary noradrenaline, plasma renin activity and plasma aldosterone were within normal limits in all patients. At hospitalization, hypertension, defined as systolic or diastolic pressure >160/90 mm Hg, was found in 11 patients and diabetes mellitus in 7. Electrocardiography and echocardiography were performed before and after operation, and followed up for periods from 3 months to 6 years and 3 months. Patients 3, 6 and 7 were lost late

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TABLE I Patient Profiles

Case	Age (yr) & Sex	Etiology	Blood Pressure on Admission (mm Hg)	SH (yrs)	75 g OGTT	DM (yrs)	Duration of Illness (yrs)
1	27F	Left adrenal adenoma	164/92	3/12	IGT pattern	0	2
2	33F	Left adrenal adenoma	154/92	0	DM pattern	2	2
3	35F	Left adrenal adenoma	158/96	0	Normal	0	3/12
4	38F	Left adrenal adenoma	160/102	1/12	DM pattern	0	2
5	42F	Pituitary microadenoma	120/76	0	DM pattern	0	1
6	43M	Bilateral adrenal adenoma	170/108	5	DM pattern	0	5
7	43F	Bilateral adrenal adenoma	166/108	10	DM pattern	3	10
8	44M	Left adrenal adenoma	164/92	6/12	IGT pattern	0	1
9	46M	Left adrenal adenoma	175/100	15	IGT pattern	0	2
10	50F	Right adrenal carcinoma	160/90	3/12	DM pattern	3/12	3
11	51M	Pituitary microadenoma	144/96	13	IGT pattern	0	5
12	57F	Left adrenal adenoma	212/136	14	DM pattern	0	14

DM = diabetes mellitus; IGT = impaired glucose tolerance; OGTT = oral glucose tolerance test; SH = systemic hypertension.

TABLE II Cardiac Characteristics Before Operation and at Late Follow-Up

Pt.	Duration of Follow-Up	Blood Pressure (mm Hg)		CTR (%)		Electrocardiographic Findings			
						SVI + RV5 (mm)		Negative T Waves	
		Before	Late	Before	Late	Before	Late	Before	Late
1	3 mos	164/92	110/50	51	39	44	36	V_{4-6}	0
2	8 mos	154/92	100/58	51	48	31	23	III	III
3	—	158/96	—	44	—	22	—	III	—
4	2 yrs, 4 mos	160/102	122/76	52	45	37	24	I, aVL, V_{1-6}	0
5	4 yrs, 3 mos	120/76	138/90	50	52	32	35	0	0
6	—	170/108	—	67	—	48	—	I, aVL, V_{4-6}	—
7	—	166/108	—	54	—	48	—	I, II, aVL, V_{3-6}	—
8	2 yrs, 5 mos	164/92	128/72	57	46	55	38	III, aVF	III
9	6 mos	175/100	130/80*	59	48	66	50	I, aVL, $V_{5,6}$	aVL
10	2 yrs, 5 mos	160/90	138/82	64	58	36	31	0	0
11	6 yrs, 3 mos	144/96	144/86	52	48	52	48	I, II, aVL, aVF, V_{3-6}	I, II, aVL, V_{3-6}
12	3 yrs, 5 mos	212/136	136/88*	61	53	52	18	I, aVL, V_{4-6}	0

*Taking antihypertensive drugs.
Before = before operation; CTR = cardiothoracic ratio; Late = late follow-up.

during follow-up: patients 6 and 7 failed to appear and patient 3 had cerebral bleeding. The thickness of the interventricular septum and the posterior wall at end-diastole, left ventricular end-diastolic dimension, left ventricular end-systolic dimension and fractional shortening were measured from 2-dimensional and M-mode echocardiographic studies. Asymmetric septal hypertrophy was defined as the ratio of the thickness of the interventricular septum to that of the posterior wall exceeding 1.3 and the thickness of interventricular septum thicker than 15 mm. The findings were compared with those of 54 patients with nontreated essential hypertension (34 men and 20 women, mean age 48 ± 9 years, range 23 to 60) and 8 patients with primary aldosteronism (3 men and 5 women, mean age 43 ± 7 years, range 30 to 53).

RESULTS

Before operation: Cardiac enlargement, defined as cardiothoracic ratio >50%, appeared on the chest x-ray films of 10 patients. Electrocardiograms showed high voltage of QRS complexes in 9 patients and negative T waves in the broad leads in 7 (Table II). In patient 1, an electrocardiogram recorded 1 year before admission was normal, but on admission negative T waves were shown in leads V_4 to V_6 (Figure 1). Left ventricular hypertrophy was seen in the echocardiograms of 9 patients, and all of them had evidence of asymmetric septal hypertrophy (Table III). All 7 patients with negative T waves in the broad leads had asymmetric septal hypertrophy. Only patient 11 had systolic anterior movement of the anterior mitral leaflet. None of the levels of the urinary 17-hydroxycorticosteroids, serum cortisol, urinary adrenaline, urinary noradrenaline, plasma aldosterone and plasma renin activity correlated with the findings of the electrocardiograms or echocardiograms. In essential hypertension, asymmetric septal hypertrophy was seen only in 5 patients (9%) and in those with primary aldosteronism it was not seen (Table IV). Cardiac catheterizations and right ventricular endomyocardial biopsies were performed in 4 patients (patients 3, 4, 11 and 12) and showed an increase in left ventricular end-diastolic pressure only in patient 11 and a decrease in left ventricular ejection fraction only in patient 4. Cardiac indexes were within normal limits in all 4 patients. On the biventriculograms, the interventricular septum was spindle-shaped only in patient 11. In patients 4, 11 and 12, the right endomyocardial biopsy specimens indicated hypertrophy of myocytes, mild degeneration of myocytes and an increase in myocardial interstitial fibrosis. Finally, only patient 11 had bizarre nuclei and disorganization of myocytes, which are thought to be specific

findings for hypertrophic cardiomyopathy. There were no abnormal pathologic findings in patient 3.

Late follow-up (Tables II and III): Nine patients could be followed up. High blood pressure persisted in 2 patients (nos. 9 and 12) who required antihypertensive therapy. The cardiothoracic ratio decreased in all patients except patient 5 and became normal in 6 patients. The high voltages of the QRS complexes decreased in all patients except patient 5 and the negative T waves reverted to normal in all patients except patient 11 (Figures 1 and 2). From the results of hormonal and roentgenographic examinations, patient 5 was diagnosed as having recurrence of pituitary adenoma. Seven of the 9 patients with asymmetric septal hypertrophy could be followed up. In 7 patients, the thickness of both the interventricular septum and the posterior wall decreased

TABLE III Echocardiographic Findings Before Operation and at Late Follow-Up

	LVDd (mm)		LVDs (mm)		FS		IVST (mm)		PWT (mm)		IVST/PWT	
Pt.	Before	Late	Before	Late	Before	Late	Before	Late	Before	Late	Before	Late
1	52	51	30	30	0.42	0.41	16	8	12	9	1.33	0.89
2	50	46	36	30	0.28	0.35	19	10	12	10	1.58	1.00
3	51	—	32	—	0.37	—	9	—	7	—	1.29	—
4	50	43	36	22	0.28	0.49	17	8	11	8	1.55	1.00
5	51	50	30	30	0.41	0.40	9	10	9	10	1.00	1.00
6	56	—	39	—	0.30	—	21	—	12	—	1.75	—
7	48	—	32	—	0.33	—	20	—	11	—	1.82	—
8	56	52	40	36	0.29	0.31	20	12	11	10	1.82	1.20
9	48	47	32	25	0.33	0.47	20	15	13	12	1.54	1.25
10	52	54	31	31	0.40	0.43	12	8	11	10	1.10	0.80
11	53	50	34	30	0.36	0.40	32	22	12	11	2.67	2.00
12	34	47	26	23	0.40	0.51	19	11	14	11	1.36	1.00

Before = before operation; FS = fractional shortening; IVST = thickness of interventricular septum at end-diastole; Late = late follow-up; LVDd = left ventricular dimension at end-diastole; LVDs = left ventricular dimension at end-systole; PWT = thickness of posterior wall at end-diastole.

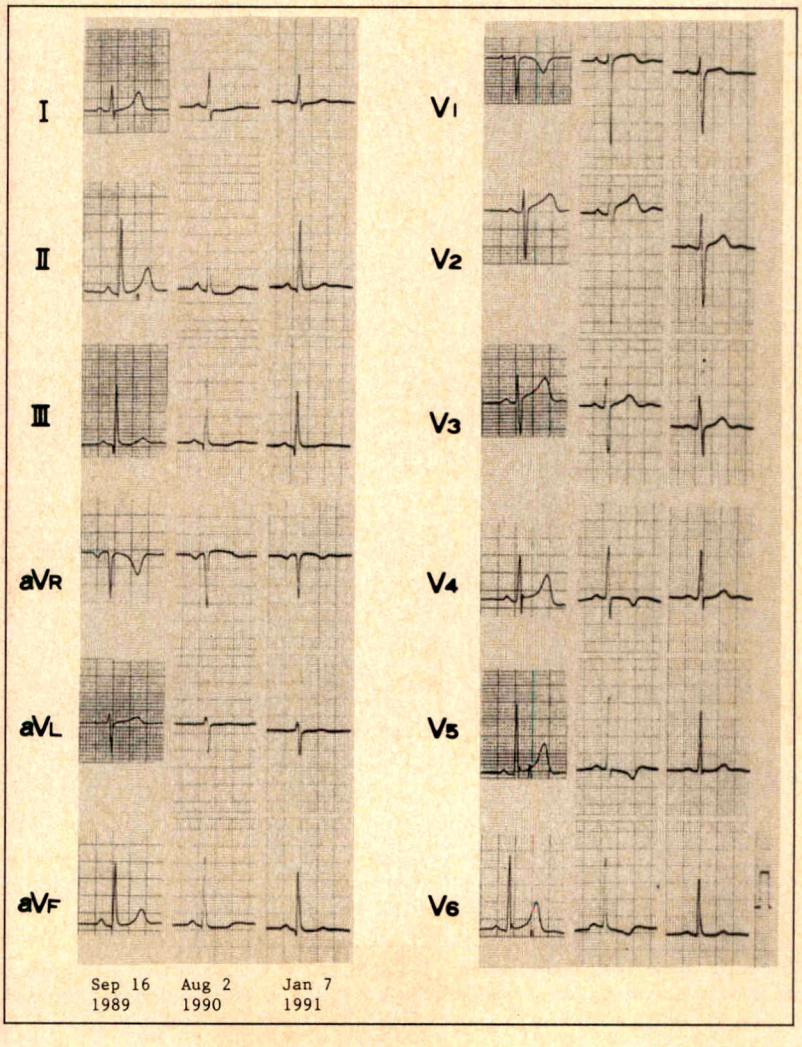


FIGURE 1. Serial electrocardiograms of patient 1. The electrocardiogram recorded about 1 year before admission showed normal results. On admission all the T waves had flattened and inverted in leads V_4 to V_6. Adrenalectomy was performed in September 1990. After the operation the inverted T waves reversed to normal.

TABLE IV Echocardiographic Findings in Cushing's Syndrome, Essential Hypertension and Primary Aldosteronism

	Cushing's Syndrome (n = 12)	Essential Hypertension (n = 53)	Primary Aldosteronism (n = 8)	p Value
Age	42 ± 8*	48 ± 9	43 ± 7	<0.05
Men/women	4/8	34/19	3/5	
IVST	17.8 ± 6.2†‡	11.5 ± 2.9	11.3 ± 1.2	<0.01
PWT	11.3 ± 1.8	10.4 ± 1.6	10.8 ± 1.5	<0.01
IVST/PWT	1.57 ± 0.44†‡	1.11 ± 0.21	1.05 ± 0.09	<0.01
IVST/PWT ≥1.3 and IVST ≥15 mm	9/12(75%)	5/53(9%)	0/8	

*p <0.05; †p <0.01 versus essential hypertension; ‡p <0.01 versus primary aldosteronism by analysis of variance followed by Scheffé's multiple comparison.
Values are mean ± standard deviation.
Abbreviations as in Table III.

and asymmetric septal hypertrophy disappeared (Figures 3 and 4). Patient 11 had a decrease in the thickness of the left ventricular walls, but the thickness of the interventricular septum was still 22 mm and asymmetric septal hypertrophy persisted 6 years after the operation. Based on the results of the echocardiographic examinations, cardiac catheterization, right ventricular endomyocardial biopsies and postoperative course, only patient 11 was diagnosed as having hypertrophic cardiomyopathy.

DISCUSSION

Our present study shows that most patients with Cushing's syndrome, especially due to adrenal adenoma, have severe left ventricular hypertrophy. Moreover, most patients with left ventricular hypertrophy have disproportional hypertrophy of the interventricular septum. Asymmetric septal hypertrophy is one of the specific findings of hypertrophic cardiomyopathy, but it may appear as a symptom of other conditions. For example, asymmetric septal hypertrophy is sometimes seen in essential hypertension but not very often. Wicker et al[3] observed it in only 11 of 613 patients. Schlant et al[4] studied 196 patients with essential hypertension and they did not find any asymmetric septal hypertrophy. There are several reports about secondary hypertension and cardiac characteristics. Vensel et al[5] reported that asymmetric septal hypertrophy was seen in only 5 of 42 patients with renovascular hypertension. Shub et al[6] studied 26 patients with pheochromocytoma and found only 1 patient with evidence of asymmetric septal hypertrophy. Suzuki et al[7] examined 19 patients with primary aldosteronism and 19 patients with renovascular hypertension, but found it in only 1 patient in each group. Moreover the mean thickness of the interventric-

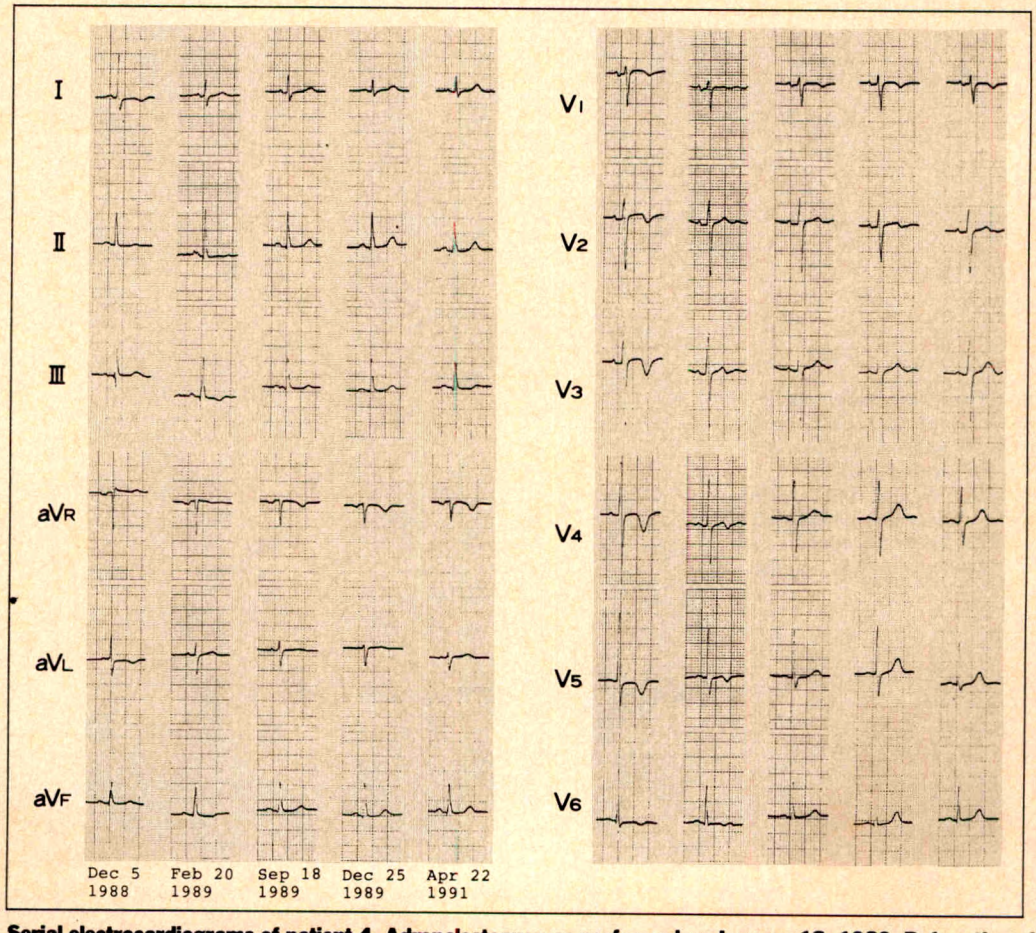
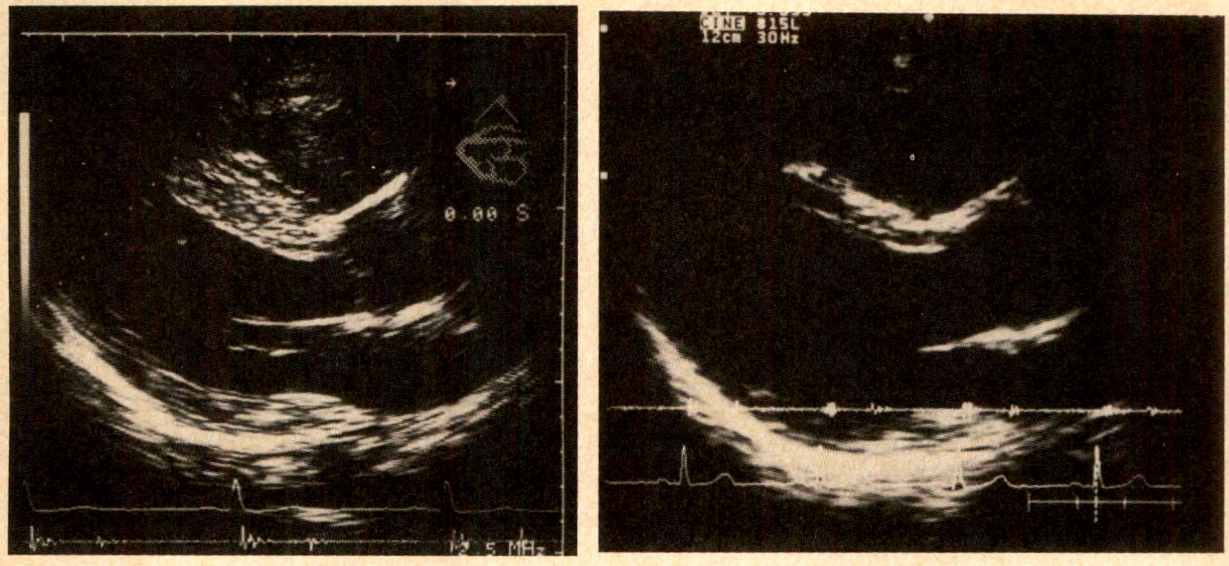


FIGURE 2. Serial electrocardiograms of patient 4. Adrenalectomy was performed on January 13, 1989. Before the adrenalectomy, inverted T waves were shown in leads I, aVL and V_1 to V_6, but these reverted to normal after the operation.

ular septum in patients with essential and other secondary hypertension was mild. In our study, the mean thicknesses of the interventricular septum were 17.8 ± 6.2, 11.5 ± 2.9 and 11.3 ± 1.2 mm in patients with Cushing's syndrome, essential hypertension and primary aldosteronism, respectively. Because of these peculiar and extreme cardiac characteristics (especially a high frequency of asymmetric septal hypertrophy, which is unusual in patients with both essential and other secondary hypertension), it is thought that other mechanisms



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FIGURE 3. Serial 2-dimensional echocardiograms of patient 4. An increased thickness of the interventricular septum and an increased ratio of the thickness of the interventricular septum to that of the posterior wall reverted to normal after the operation.

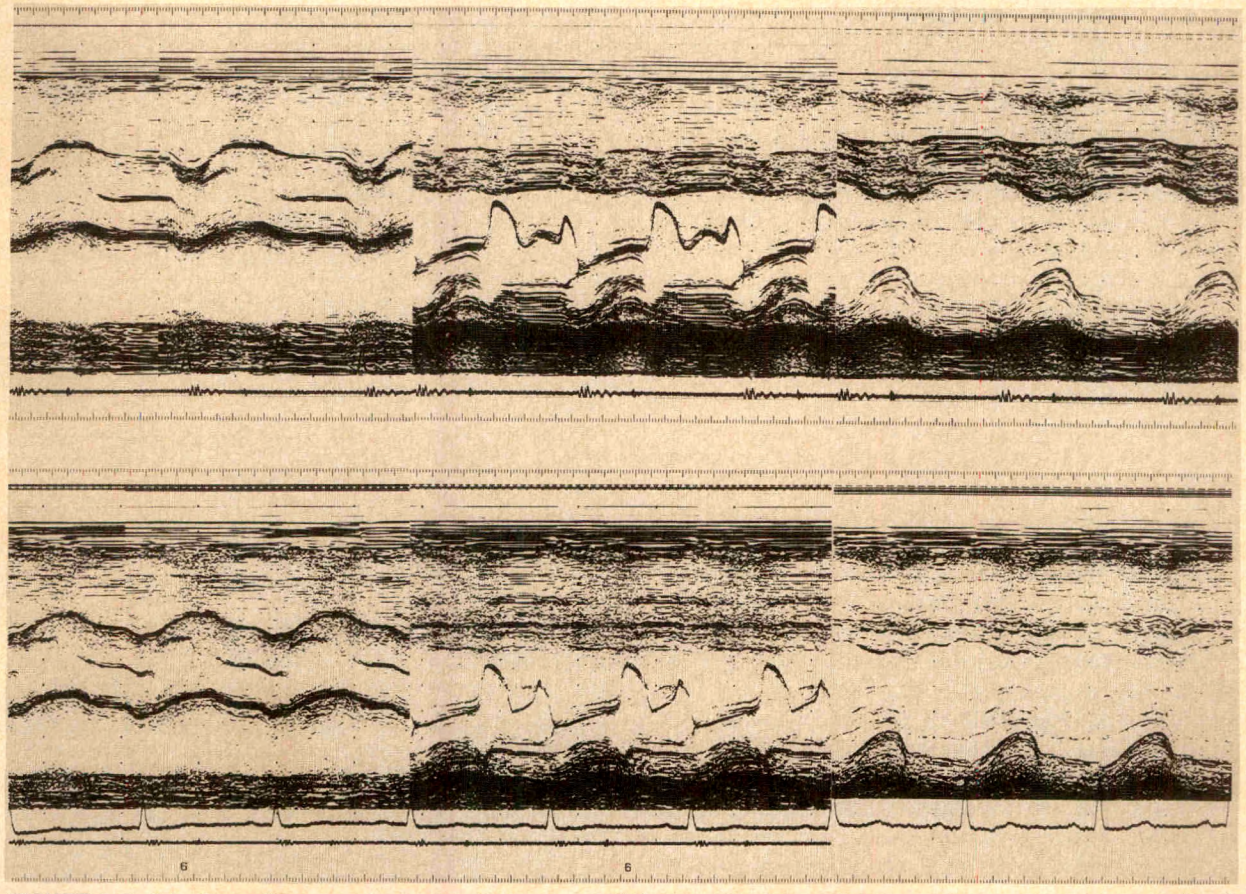


FIGURE 4. Serial echocardiograms of patient 1. An increased thickness of the interventricular septum and an increased ratio of the thickness of the interventricular septum to that of the posterior wall reverted to normal after the operation.

in addition to increased aortic pressure cause left ventricular hypertrophy in Cushing's syndrome. Alpert[8] suggested that hydrocortisone therapy may produce left ventricular hypertrophy without hypertension, similar to hypertrophic cardiomyopathy. Excessive plasma cortisol in Cushing's syndrome is thought to be 1 cause of left ventricular hypertrophy. In follow-up studies after the operations, all patients except patient 11, who appeared to have hypertrophic cardiomyopathy, have complete regression of the thickness of the left ventricular wall. The mean thickness of the interventricular septum and posterior wall decreased from 17.0 ± 4.1 and 11.7 ± 1.4 to 10.6 ± 2.4 and 10.1 ± 1.2 mm, respectively. Whereas regression of left ventricular hypertrophy as such has been well documented,[9-13] reports of such complete regression are rare. After the operation, increased aortic pressure persisted in 2 patients, and returned to within normal range in the remaining 7 patients. Neither postoperative high aortic pressure nor complicated diabetes mellitus correlate with this regression of wall thickness.

The reasons why left ventricular hypertrophy in Cushing's syndrome is severe remain unknown. Because severe left ventricular hypertrophy is uncommon in patients with primary aldosteronism, pheochromocytoma and renovascular hypertension, mineralocorticoid actions, circulating catechoramines and plasma renin activity are not thought to be the pathogenetic factors of ventricular hypertrophy in Cushing's syndrome. Recently, evidence of independently functioning local renin-angiotensin systems in a number of tissues including heart muscle has been established. Renin, angiotensin and its binding site as well as angiotensin-converting enzyme have all been demonstrated in the heart, and in situ hybridization histochemistry demonstrate that both renin and angiotensinogen messenger ribonucleic acid are expressed in the atrial and ventricular myocytes.[14-18] Angiotensin produced by the endogenous tissue renin-angiotensin system may exert an autocrine or paracrine influence, or both, on local tissue. It is further hypothesized that local angiotensin in heart muscle may be involved with myocardial protein synthesis, cell growth and the development of ventricular hypertrophy. It is unknown, however, how excessive cortisol affects the local renin-angiotensin system. In 1973, Krakoff[19] reported that significant elevations of plasma renin substrate were observed in subjects with Cushing's syndrome, who had undergone glucocorticosteroid therapy and taken oral contraceptive agents or estrogen. In 1986, Saruta et al[20] also reported plasma renin substrate elevation and plasma renin activity were not suppressed in patients with Cushing's syndrome. These effects of cortisol may affect the local renin-angiotensin system and generate ventricular hypertrophy. Further study is needed to assess the role of the local renin-angiotensin system in the heart in patients with Cushing's syndrome and in patients treated with glucocorticosteroid therapy.

The preoperative endomyocardial biopsies suggest that increased myocardial fibrosis had occurred in some patients. Increased myocardial fibrosis is a nonspecific finding and frequently seen in hypertensive hearts.[21] It is not clear whether only high aortic pressure induces myocardial fibrosis or excessive cortisol may also play some part.

If long-term excess of glucocorticoids produces severe left ventricular hypertrophy, patients with other diseases such as nephrotic syndrome or collagen disease undergoing long-term treatment with large doses of glucocorticoids may also be affected and may easily develop congestive heart failure. Such disorders always complicate hypertension or renal failure. Thus, it is difficult to determine whether excessive glucocorticoids affects cardiac performance in such patients. Additional treatments, such as angiotensin-converting enzyme inhibitors or β blockades may be necessary for patients with these conditions.

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Effect of Balloon Material on Coronary Angioplasty

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Since its introduction in 1977, coronary balloon angioplasty has gained wide acceptance as a nonsurgical approach to myocardial revascularization. There have been many important technologic advances in angioplasty equipment and significant improvements in balloon dilatation systems.[1] These technologic advances have led to a greater choice in balloon materials, and to controversy regarding the effect of balloon composition on angioplasty outcomes. It has recently been suggested that compliant balloons lead to more frequent coronary artery intimal dissection.[2] Coronary artery dissection leads to increased angioplasty complications.[3] If a specific balloon material increases the risk of coronary dissection, then there is the potential for important adverse patient outcomes. Therefore, this study was designed to evaluate the effect of balloon material, in particular balloon compliance, on the frequency and severity of coronary dissection. We also sought to examine the effect of balloon material on other angiographic and clinical outcomes.

Consecutive elective, 1-vessel, single site cases were included in the analysis during the study period January 1, 1990, to April 1, 1991. Of 1,414 segments dilated, 1,370 were treated with 1 balloon material and therefore met the inclusion criteria for this analysis. Segment sites at total occlusion and vein grafts were excluded from analysis. Patients undergoing coronary angioplasty at our institution are prospectively enrolled in a database at the time of the procedure. Included are patient's clinical characteristics, angiographic features of the dilated artery, and equipment used for dilatation. Coronary angioplasty was performed using standard technique. Balloon size was selected to provide a nearly 1.0:1 balloon to artery ratio. Balloon materials included in this analysis were: polyethylene, polyethylene terapthelate and polyolefin copolymer. Each of these materials represent a category of balloon material compliance: polyethylene terapthelate, none (<3% from 6 to 10 atm); polyethylene, somewhat compliant (8% from 6 to 10 atm); and polyolefin copolymer, compliant (14% from 6 to 10 atm). For the purpose of the current study, areas of coronary dilatation that required only 1 of these balloon materials for successful dilatation were included for analysis. Balloon type was then correlated with patient angiographic and clinical outcome.

Technical success was defined as <50% residual stenosis after angioplasty, and clinical success was defined as technical success in dilating the culprit lesion plus absence of major complications or anginal pain on discharge.

Coronary dissections were categorized using the National Heart, Lung, and Blood Institute classification system for intimal tears, developed by the Coronary Angioplasty Registry. Type A dissections represent radiolucent areas within the coronary lumen during contrast injection. This was considered a nonsignificant angiographic finding after angioplasty and was not included in the study. Type B dissections are parallel tracks or double lumen separated by a radiolucent area during contrast injection. Type C dissections appear angiographically as contrast outside the coronary lumen, with persistence of contrast in the area after clearance of dye from the coronary lumen. Type D dissections represent spiral luminal filling defects, frequently with extensive contrast staining of the vessel. Type E dissections appear as new, persistent filling defects. Type F dissections represent those that lead to total occlusion of the coronary artery, without distal anterograde flow. As proposed by the Coronary Angioplasty Registry, types E and F dissections may be caused by thrombus.

Differences in categorical data were analyzed using chi-square analysis and differences in continuous variables were analyzed using Student's t *test. A p value <0.05 was accepted as statistically significant. Analysis were performed on an IBM computer using SAS statistical packages.*

Analysis of each cohort revealed that the patients were similar with respect to demographic data, clinical presentation and lesion morphology before coronary angioplasty (Table I). Despite differences in balloon compliance, the balloon to artery ratio was not significantly different for each cohort (polyethylene, 1.07:1; polyethylene terapthelate, 1.05:1; and polyolefin copolymer, 1.09:1).

TABLE I Clinical, Angiographic and Procedure Profile

Variables	Polyethylene (n = 718) No. (%)	Polyethylene Terapthelate (n = 318) No. (%)	Polyolefin Copolymer (n = 334) No. (%)
Clinical variables			
Sex (men)	503 (70)	229 (72)	230 (69)
Age	41 (64)	200 (63)	214 (64)
Unstable angina	359 (50)	169 (53)	174 (52)
Lesion characteristics			
Concentric	108 (15)	57 (18)	57 (17)
Eccentric	539 (75)	241 (76)	251 (75)
Lesion length	8.2 ± 4.8	7.9 ± 4.6	8.4 ± 4.9
Thrombus present	101 (14)	38 (12)	50 (15)
Angle >90	86 (12)	32 (10)	43 (13)
Procedure variables			
Inflation duration (sec)	102 ± 71	110 ± 68	104 ± 74
Peak atmospheres	8.7 ± 2.3	10.4 ± 68	8.01 ± 2.5
Balloon:artery ratio	1.07:1	1.05:1	1.09:1

p = not significant for all variables.

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TABLE II Incidence and Severity of Coronary Dissection

NHLBI Dissection Type	Polyethylene 600 (n = 718) No. (%)	Polyethylene Terapthelate (n = 318) No. (%)	Polyolefin Copolymer (n = 334) No. (%)
B	149 (21)	46 (14)	55 (17)
C	17 (2.4)	8 (2.6)	13 (4)
D	11 (1.5)	2 (0.6)	4 (1)
E	3 (0.4)	0 (0)	1 (0.3)
F	4 (0.6)	1 (0.3)	1 (0.3)
None	534 (74)	261 (82)	260 (78)

p = not significant for all variables.
NHLBI = National Heart, Lung, and Blood Institute.

TABLE III Angiographic and Clinical Outcome

	Polyethylene 600 (n = 718) No. (%)	Polyethylene Teraphelate (n = 318) No. (%)	Polyolefin Copolymer (n = 334) No. (%)
Technical success	669 (93)	302 (95)	312 (93)
Clinical success	666 (93)	305 (98)	314 (94)
Emergency bypass surgery	14 (1.9)	5 (1.7)	4 (1.3)
Myocardial infarction	9 (1.4)	4 (1.3)	0 (0)
Acute artery closure	29 (4.1)	8 (2.6)	11 (3.4)
Death	14 (1.9)	0 (0)	5 (1.7)

p = not significant for all variables.
Death = all in-hospital deaths, angioplasty or non–procedure-related

The frequency of coronary artery dissection and severity of dissections appeared no more frequent with any particular balloon material used (Table II). When each subtype of dissection is analyzed there is no difference between balloon material cohorts. If the types of dissection (B to F) are pooled and compared again there are no significant differences.

Clinical outcomes and in-hospital complications were also compared with balloon material. Technical success, clinical success, emergency surgery, Q-wave myocardial infarction, death and abrupt closure were analyzed and found unrelated to balloon material (Table III). The frequency of adverse patient outcomes were nearly identical between the groups of patients treated with different balloon materials.

This study was nonrandomized and retrospective. The choice for balloon material usage was determined by operator preference. It is possible that a given balloon material was used more frequently in a high-risk group of patients and that this bias might mask an advantage for that balloon material. It is also possible that given subsets of patients would be best managed by a specific balloon material. This study does not address this issue and reflects outcomes on a larger, more generalized population of patients undergoing angioplasty.

Lesion morphology, clinical presentation and procedural variables have been reported as correlates to coronary dissection.[4,5] The presence of intimal dissection is strongly correlated with acute ischemic events. Furthermore, the extent of dissection is highly predictive of in-hospital major complications.[6] Technique and materials should therefore be selected to minimize coronary dissection. It has been suggested that compliant balloons are more likely to cause dissection and that the "dumbbell" effect may be exaggerated with higher inflation pressures leading to dissection of the adjacent normal artery. This theoretical concern was not supported by our data. Furthermore, the angiographic results were validated by nearly identical rates of adverse patient outcomes. Operators should therefore choose among the various balloon materials based on performance and preference factors as opposed to an intrinsic safety issue.

Acknowledgment: We thank Barb Kummer and Ellen Sawicki, RN, BS, for data collection, Lori Kilber, BS, for data entry, Howard Liang, MS, for statistical analysis, and Denise Evans for assistance in the preparation of this brief report.

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Extent and Severity of Abnormal Left Ventricular Wall Motion Detected by Exercise Echocardiography During Painful and Silent Ischemia

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Myocardial ischemia occurs in the absence of symptoms in a proportion of patients with coronary artery disease, a phenomenon that may reflect disturbed pain responsiveness.[1] Episodes of painless ("silent") ischemia are frequent even in patients who have angina at other times,[2] suggesting that some features of the ischemic event, rather than the patient, may be responsible for the absence of pain. One possible explanation is that the occurrence of pain relates to the extent or severity of ischemia. The relation of angina to the amount of left ventricular dysfunction has been debated, with evidence in favor[3] and against[4,5] a positive correlation. This study compared the severity and extent of ischemia, assessed by exercise echocardiography, with the presence of angina.

Seventy-one consecutive patients with significant coronary artery disease, and ischemic left ventricular wall motion disturbances at exercise echocardiography were studied. The group comprised 64 men and 7 women (mean age 59 ± 9 years). A previous Q-wave myocardial infarction was present in 30 patients. All patients underwent maximal, symptom-limited treadmill exercise testing by 12-lead electrocardiography and standard monitoring and end points. The results were read by an experienced observer unaware of the results of exercise echocardiography; a positive test result was defined by planar or downsloping ST depression of >1 mm. Factors producing a nondiagnostic exercise electrocardiogram (resting ST-segment changes, left bundle branch block, left ventricular hypertrophy with strain, and so forth) were noted, and ST-segment changes in the presence of these were identified as nondiagnostic.

Exercise echocardiographic images were acquired in the lateral decubitus position before and immediately after treadmill exercise using standard, commercially available echocardiographic equipment and on-line image digitization (Prevue, Nova Microsonics, Indianapolis, Indiana). Images were archived in a quad-screen, cine-loop digitized format (on 5 ¼-inch discs), and were also recorded on ½-inch videotape for subsequent blinded review by ≥2 observers. The interpretation of stress echocardiographic images was assisted by the use of a previously validated, qualitative analysis system (1 = normal, 2 = hypokinesia, 3 = akinesia, and 4 = dyskinesia) of 16 myocardial segments. Infarction was defined by the presence of akinesia or dyskinesia at rest. Ischemia was identified by delayed contraction, failure to exhibit exercise-induced hyperkinesia, or deterioration of regional wall motion.[6] The extent of ischemia was defined by the number of involved segments, and the extent of severe ischemia was derived from the number of segments developing akinesia or dyskinesia with stress. The maximal severity of ischemia was determined by the greatest reduction of wall motion score in any segment. Finally, to compensate for the presence and extent of infarction, the number of ischemic segments was assessed as a proportion of the number of viable myocardial regions.

Silent ischemia occurred in 48 patients (68%). This group was compared with patients who had anginal symptoms (Table I). Patients with silent ischemia showed no difference from the remaining patients with respect to age, gender, medical therapy, past myocardial infarction or number of diseased vessels. Exercise parameters were similar in both groups. Of the patients with silent ischemia, 18 had nondiagnostic electrocardiographic changes, and 19 of the remaining 30 patients (63%) showed ST-segment changes; in contrast, 14 of 17 patients (82%) with angina and an interpretable electrocardiogram showed ischemia by these criteria (p = not significant).

The number of segments identified as ischemic by exercise echocardiography was 3.7 ± 2.0 in the silent ischemia group, and 4.1 ± 1.9 in those with angina (p = not significant). The number of segments developing severe ischemia was also not significantly different (1.4 ± 1.6 for the silent ischemia group, and 1.3 ± 1.4 for the anginal group). The maximal severity of ischemia (evidenced by the greatest deterioration of wall motion)

TABLE I Clinical, Exercise and Echocardiographic Parameters in Patients with Significant Coronary Disease, and Silent and Painful Ischemia at Exercise Echocardiography*

	Silent	Angina
Age (years)	60 ± 9	57 ± 9
Male gender (%)	39 (81%)	19 (83%)
Drug therapy (%)	39 (81%)	17 (74%)
Previous myocardial infarction (%)	21 (44%)	9 (39%)
1-vessel coronary disease (%)	28 (58%)	12 (52%)
Percent age-predicted max. heart rate	87 ± 11	88 ± 8
Peak rate-pressure product (×10³)	22.5 ± 5.2	23.4 ± 5.6
Exercise capacity (METS)	6.0 ± 2.6	7.1 ± 2.8
No. of ischemic segments	3.7 ± 2.0	4.1 ± 1.9
No. of segments with severe ischemia	1.4 ± 1.6	1.3 ± 1.4
Maximal severity of ischemia	1.4 ± 0.8	1.7 ± 0.9
Percentage of noninfarcted LV developing ischemia	29 ± 16	29 ± 14

*No significant difference between the groups is apparent with respect to any parameter.
LV = left ventricular; max. = maximal.

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was 1.4 ± 0.8 in the silent ischemia and 1.7 ± 0.9 in the anginal group (p = not significant). Infarct regions accounted for 2.5 ± 2.8 and 1.6 ± 1.8 segments, respectively (p = not significant). Moreover, the "ischemic index" (conceived in order to compensate for the presence and extent of infarction) also showed no significant difference in the proportion of noninfarcted myocardium showing evidence for ischemia in the groups with and without angina. Even with the exclusion of patients without ST-segment changes, patients with silent ischemia (n = 19) and those with angina (n = 14) did not differ with respect to the number of ischemic segments (4.3 ± 2.1 vs 3.5 ± 1.7) or the number of severely ischemic segments (1.5 ± 1.9 vs 1.5 ± 1.6).

Some previous reports have failed to show any relation between the occurrence of anginal pain and the severity of exercise-induced left ventricular dysfunction.[4,5] These studies, however, may be criticized on a methodologic basis; the use of gated nuclear ventriculography may have precluded accurate analysis of the severity of regional dysfunction, with attention being paid to global ejection fraction. In contrast, other reports have demonstrated a correlation between symptoms and the severity of ischemia. The use of first-pass nuclear ventriculography facilitates better appreciation of regional function; Iskandrian and Hakki[3] found angina to correlate with more severe deterioration of regional function, using the first-pass methodology. Unfortunately, this technique does not permit the examination of all myocardial regions, so that a correlation between angina and the extent of ischemia was not possible. Greater hemodynamic disturbances have been reported in the presence of painful versus silent ischemia in the setting of unstable angina,[7] but whether this reflected greater severity or extent of ischemia is unclear.

Exercise echocardiography offers both good resolution of regional wall motion (not available with gated nuclear imaging), and multiplane imaging (not available with first-pass nuclear studies). The results of this study indicate that exertional angina is unrelated to the occurrence of electrocardiographic changes of ischemia, the degree of deterioration of regional function, or to the number of ischemic segments involved. Thus, angina appears to be unrelated to the extent or severity of ischemia, defined by exercise echocardiography. These findings suggest that characteristics of the ischemic event are not major determinants of the presence or absence of exertional angina.

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Clinical Significance of Abrupt Vasodepression During Dobutamine Stress Echocardiography

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Dobutamine stress together with 2-dimensional echocardiography for identification of ischemia-induced wall motion abnormalities is emerging as an accurate method of detecting coronary artery disease.[1] In a different clinical setting, exogenous catecholamine infusion during upright tilt testing has been used to elicit symptomatic hypotension and bradycardia in patients with recurrent syncope of unknown origin.[2] This followed the observation that increases in heart rate and arterial pressure,[3] and elevated circulating catecholamine levels[4] frequently precede vasovagal reactions implicating transient heightened sympathoadrenal activity before vasodepression. Hypotension during exercise is recognized as a marker for severe coronary disease and poor prognosis, which is seen in patients with a dilated, poorly functioning left ventricle due to extensive new regional asynergy on post-treadmill exercise echocardiography.[5] We describe instances of paradoxical hypotension-bradycardia in patients undergoing dobutamine stress echocardiography for suspected coronary disease, comment on its clinical significance and recommend precautions to maximize test safety.

We studied 50 patients (44 men and 6 women, aged 54 ± 9 years) awaiting cardiac catheterization for suspected coronary disease after pharmacologic washout of cardioactive treatment. Dobutamine stress echocardiography was performed with patients semirecumbent, using an 8-minute stepwise infusion of 5, 10, 15 and 20 μg/kg/min during 2-dimensional echocardiographic imaging of the parasternal long-axis, short-axis and apical 4- and 2-chamber views (Toshiba SSH-160A, 3.75 MHz transducer). Heart rate and electrocardiographic monitoring was continuous, and blood pressure was measured every 1 to 2 minutes using a Critikon, Dinamap vital signs monitor. Previously reported end points were

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This study was funded by Grant 3/90 from the Coronary Artery Disease Research Association, London, United Kingdom. Additional support was obtained from Eli Lilly and Company Limited, Basingstoke, Hampshire, United Kingdom. Dr. Mazeika is a Coronary Artery Disease Research Association Research Fellow. Manuscript received October 8, 1991; revised manuscript received January 31, 1992, and accepted February 2, 1992.

used,[1] and the induction of transient regional asynergy defined an abnormal study.

Presyncope was defined as premonitory symptoms of imminent syncope, and a hypotensive response as a >20 mm Hg decrease in systolic pressure or a lesser reduction associated with presyncope. After documentation of vasodepression, we reviewed the clinical, investigative and stress echocardiographic data in all patients and followed up those with hypotension to establish the clinical significance of this reaction.

All patients also underwent a modified Bruce exercise electrocardiogram without antianginal medication using conventional end points. Coronary angiography was performed by the femoral approach; a ≥70% diameter stenosis in ≥1 major epicardial vessel was considered significant.

Continuous data are expressed as mean ± SD. Parametric statistics and the Yates' corrected chi-square test were used, as appropriate. A p value <0.05 was considered statistically significant. The protocol was approved by the hospital ethics committee, and all patients gave informed consent.

Seven patients (14%) had a hypotensive response that occurred after a mean infusion duration of 27 ± 3 minutes (Table I and Figure 1). The mean maximum decreases in systolic arterial pressure and heart rate were 49 ± 23 mm Hg and 21 ± 11 beats/min, respectively, and followed mean increases of 29 ± 22 mm Hg and 45 ± 10

TABLE I Clinical Data, Hemodynamic Changes and Echocardiographic Findings in Seven Patients Who Manifested an Abrupt Hypotensive Response to Dobutamine Stress

Case No.	Age (yr) & Sex	Maximum SAP Decrease (mm Hg)*	Maximum HR Decrease (beats/min)*	Preceding SAP Increase (mm Hg)*	Preceding HR Increase (beats/min)*	Presyncope	Junctional Rhythm	Coronary Artery Disease (vessel)	Transient Regional Asynergy†
1	55F	28	30	5	48	+	+	0	0
2	50M	19	23	65	47	+	0	0	0
3	63M	41	16	23	55	+	0	0	0
4	53M	78	1	36	31	+	0	1 VD (LAD)	0
5	59M	39	16	2	36	+	0	2 VD (LAD, LC)	Anterior
6	58M	61	26	39	58	0	+	1 VD (LAD)	Anterior
7	66M	77	33	36	41	+	+	1 VD (right)	Inferior

*Vasodepression occurred at peak infustion rate in 6 patients and at 15 μg/kg/min in case 7.
†Wall motion pretest was normal in all patients, except case 5 who had localized lateral akinesis.
Heart rate and systolic arterial pressure at baseline were 70 ± 10 beats/min and 141 ± 8 mm Hg, respectively.
HR = heart rate; LAD = left anterior descending coronary artery; LC = left circumflex coronary artery; SAP = systolic arterial pressure; VD = vessel disease; + = present; 0 = absent.

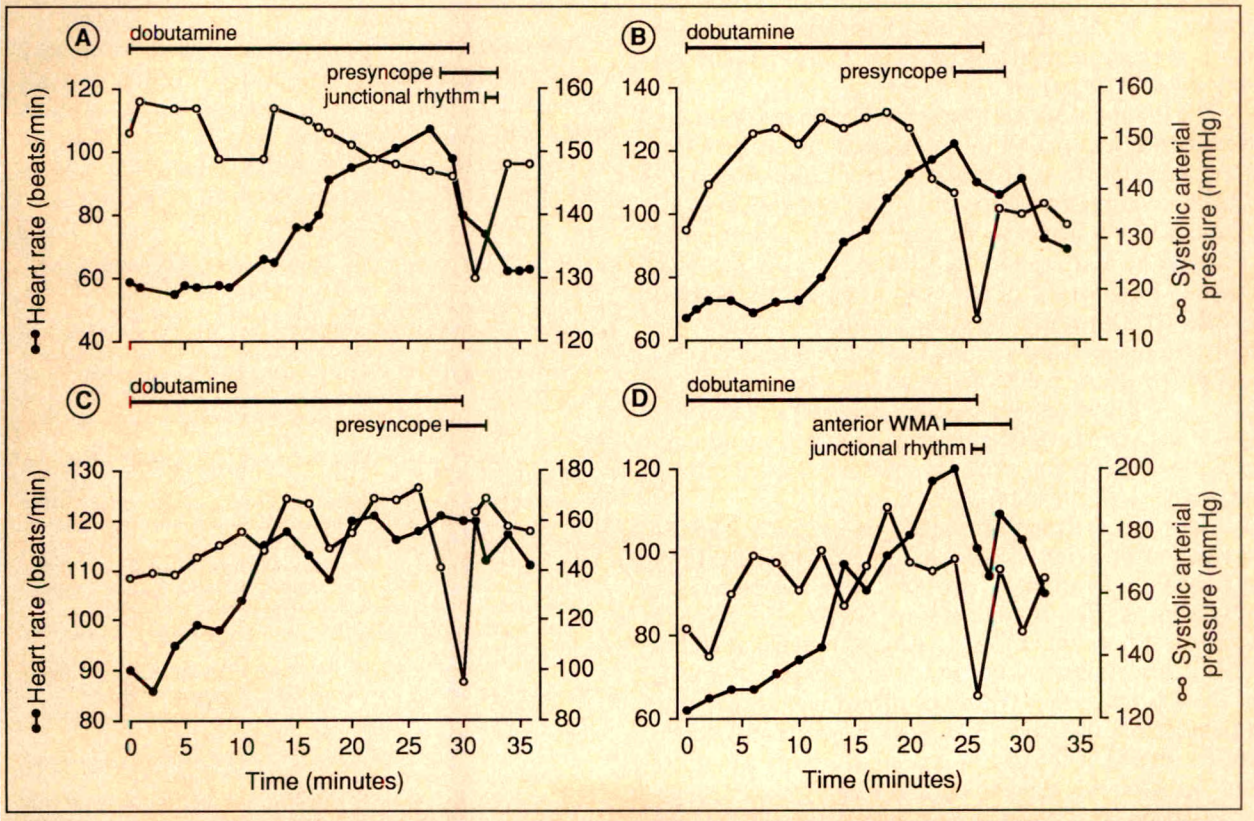


FIGURE 1. Heart rate and systolic arterial pressure response to dobutamine infusion in cases 1 *(A)*, 3 *(B)*, 4 *(C)* and 6 *(D)* (Table I). *Axis to left of each graph* refers to heart rate, and that to *right* indicates systolic arterial pressure. Note absence of reduction in heart rate during vasodepression in case 4. *Solid bars* indicate duration of stated event. WMA = wall motion abnormality.

beats/min, respectively. Minor reductions in blood pressure preceded the main reaction in cases 1, 4, 5, 6 and 7 (Figure 1). Peak heart rate, systolic blood pressure and double product during dobutamine were similar in patients with and without vasodepression (p = not significant [NS]). Symptoms resolved, and hemodynamics normalized rapidly on test termination that was necessary in all except case 2, although the patient with the worst reaction (case 7) also needed supine positioning and intravenous atropine (0.6 mg).

There were no significant differences in age (58 ± 6 vs 54 ± 9 years) or gender ratio between patients with and without vasodepression. Two of 50 patients gave a current (case 7) or remote (case 1) history of unexplained syncope. A similar proportion of patients with normal coronaries (3 of 14; 21%) and coronary artery disease (4 of 36; 11%) had a hypotensive response (p = NS). Echocardiography revealed transient regional asynergy in 3 of 7 patients (43%, all had coronary disease) with vasodepression compared with 21 of 43 (49%) of the others (p = NS). Global left ventricular function was good or vigorous in all 7 cases before and during the reaction. Furthermore, 3 (43%; cases 1, 2 and 7) of these patients had a vasovagal episode needing atropine at cardiac catheterization compared with 1 of 43 (2%) of the others (p = 0.004). One of 50 patients (case 7) manifested a hypotensive response to exercise; angina and electrocardiographic evidence of inferior ischemia during exercise were followed by severe hypotension-bradycardia with syncope in the recovery phase. No patient with vasodepression experienced cardiovascular morbidity or mortality over a total follow-up period of 121 months (range 15 to 20), although case 6 subsequently underwent coronary angioplasty, and case 5 had coronary artery bypass surgery.

The inotropic, chronotropic and pressor effects of dobutamine are mediated by stimulation of β_1, β_2 and α_1 adrenoceptors.[6] In the peripheral vasculature, β_2 and α_1-mediated vasomotor effects cancel out, and systemic vascular resistance decreases largely by a reflex withdrawal of sympathetic tone in response to an increasing cardiac output. We observed hypotension in the setting of good global left ventricular function implicating abrupt systemic vasodilation and cardiac slowing. Patients with coronary disease or inducible asynergy were as likely to develop hypotension as were the other subjects, and follow-up suggested a good prognosis. This reaction appears to represent a ceiling to the myocardial stressor effects attainable with dobutamine.

The features described suggest that a cardiovascular vasodepressor reflex is operative. Neurally mediated hypotension-bradycardia is believed to be a frequent cause of syncope that on the basis of work in animal models has been ascribed to the activation of cardiac vagal afferents innervating mechanoreceptors in the inferoposterior wall of the left ventricle.[7,8] Vigorous myocardial contraction around a small chamber (conditions present during dobutamine stress) is thought to trigger sympathoinhibition and increased parasympathetic discharge. Patients prone to vasodepression may have exaggerated cardiac mechanoreflex activity perhaps due to mechanoreceptor hypersensitivity, or altered β-receptor affinity or numbers.[8] Whether β-blockade or atropine co-administration prevents dobutamine-induced hypotension is unknown and warrants further study, although the former maneuver would probably have the disadvantage of reducing test sensitivity.[1]

The associated vasovagal episodes at cardiac catheterization may be similarly mediated, perhaps triggered directly after arteriography of the dominant vessel or provoked by increased endogenous catecholamines due to pain or fear.[7,9,10] Postexercise hypotension (as in case 7) has also been considered to be a vasovagal reaction,[11] although ischemia-induced bradycardia is a possible alternative explanation in our patient. Interestingly, hypotension is seen in patients with pheochromocytoma and is now no longer attributed to intravascular volume depletion.[12] Tan et al[13] did not observe vasodepression in patients with heart failure undergoing assessment of pump function using dobutamine, a finding consistent with evidence indicating impaired cardiac vagal afferent nerves in this condition.[8] None of our patients had poor left ventricular function.

In conclusion we found that vasodepression during dobutamine stress echocardiography is not a marker for coronary artery disease, transient asynergy or global left ventricular dysfunction. The association with hypotension-bradycardia at cardiac catheterization suggests it may identify patients with a latent or manifest susceptibility to vasovagal episodes. We recommend that atropine should be available and that test termination should be considered if systolic arterial pressure decreases by >30 or to <100 mm Hg. These findings need confirmation in larger studies.

Acknowledgment: We are grateful to the Coronary Artery Disease Research Association, London, and Eli Lilly and Company Limited, Basingstoke, Hampshire, United Kingdom, for financial support. We also thank Senka Dinarevic, MD, Mohammed Khan, MD, and Jo Joshi, BSc (Hon), for expert technical assistance.

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Elderly Patients or Patients with Impaired Liver Function: Patients over 65 years of age or patients with impaired liver function may have elevated plasma concentrations of felodipine and may therefore respond to lower doses of PLENDIL. These patients should have their blood pressure monitored closely during dosage adjustment of PLENDIL and should rarely require doses above 10 mg. (See CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION.)

Peripheral Edema: Peripheral edema, generally mild and not associated with generalized fluid retention, was the most common adverse event in the clinical trials. The incidence of peripheral edema was both dose- and age-dependent. Frequency of peripheral edema ranged from about 10 percent in patients under 50 years of age taking 5 mg daily to about 30 percent in those over 60 years of age taking 20 mg daily. This adverse effect generally occurs within 2-3 weeks of the initiation of treatment.

Information for Patients: Patients should be instructed to take PLENDIL whole and not to crush or chew the tablets. They should be told that mild gingival hyperplasia (gum swelling) has been reported. Good dental hygiene decreases its incidence and severity.

NOTE: As with many other drugs, certain advice to patients being treated with PLENDIL is warranted. This information is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects.

Drug Interactions: ***Beta-Blocking Agents:*** A pharmacokinetic study of felodipine in conjunction with metoprolol demonstrated no significant effects on the pharmacokinetics of felodipine. The AUC and C_{max} of metoprolol, however, were increased approximately 31 and 38 percent, respectively. In controlled clinical trials, however, beta-blockers including metoprolol were concurrently administered with felodipine and were well tolerated.

Cimetidine: In healthy subjects pharmacokinetic studies showed an approximately 50 percent increase in the area under the plasma concentration time curve (AUC) as well as the C_{max} of felodipine when given concomitantly with cimetidine. It is anticipated that a clinically significant interaction may occur in some hypertensive patients. Therefore, it is recommended that low doses of PLENDIL be used when given concomitantly with cimetidine.

Digoxin: When given concomitantly with felodipine the peak plasma concentration of digoxin was significantly increased. There was, however, no significant change in the AUC of digoxin.

Other Concomitant Therapy: In healthy subjects there were no clinically significant interactions when felodipine was given concomitantly with indomethacin or spironolactone.

Interaction with Food: See CLINICAL PHARMACOLOGY, *Pharmacokinetics and Metabolism.*

Carcinogenesis, Mutagenesis, Impairment of Fertility: In a two-year carcinogenicity study in rats fed felodipine at doses of 7.7, 23.1 or 69.3 mg/kg/day (up to 28 times* the maximum recommended human dose on a mg/m² basis), a dose-related increase in the incidence of benign interstitial cell tumors of the testes (Leydig cell tumors) was observed in treated male rats. These tumors were not observed in a similar study in mice at doses up to 138.6 mg/kg/day (28* times the maximum recommended human dose on a mg/m² basis). Felodipine, at the doses employed in the two-year rat study, has been shown to lower testicular testosterone and to produce a corresponding increase in serum luteinizing hormone in rats. The Leydig cell tumor development is possibly secondary to these hormonal effects which have not been observed in man.

In this same rat study a dose-related increase in the incidence of focal squamous cell hyperplasia compared to control was observed in the esophageal groove of male and female rats in all dose groups. No other drug-related esophageal or gastric pathology was observed in the rats or with chronic administration in mice and dogs. The latter species, like man, has no anatomical structure comparable to the esophageal groove.

Felodipine was not carcinogenic when fed to mice at doses of up to 138.6 mg/kg/day (28 times* the maximum recommended human dose on a mg/m² basis) for periods of up to 80 weeks in males and 99 weeks in females.

Felodipine did not display any mutagenic activity *in vitro* in the Ames microbial mutagenicity test or in the mouse lymphoma forward mutation assay. No clastogenic potential was seen *in vivo* in the mouse micronucleus test at oral doses up to 2500 mg/kg (506 times* the maximum recommended human dose on a mg/m² basis) or *in vitro* in a human lymphocyte chromosome aberration assay.

A fertility study in which male and female rats were administered doses of 3.8, 9.6 or 26.9 mg/kg/day showed no significant effect of felodipine on reproductive performance.

Pregnancy: ***Pregnancy Category C:*** *Teratogenic Effects:* Studies in pregnant rabbits administered doses of 0.46, 1.2, 2.3 and 4.6 mg/kg/day (from 0.4 to 4 times* the maximum recommended human dose on a mg/m² basis) showed digital anomalies consisting of reduction in size and degree of ossification of the terminal phalanges in the fetuses. The frequency and severity of the changes appeared dose-related and were noted even at the lowest dose. These changes have been shown to occur with other members of the dihydropyridine class and are possibly a result of compromised uterine blood flow. Similar fetal anomalies were not observed in rats given felodipine.

In a teratology study in cynomolgus monkeys no reduction in the size of the terminal phalanges was observed but an abnormal position of the distal phalanges was noted in about 40 percent of the fetuses.

Nonteratogenic Effects: A prolongation of parturition with difficult labor and an increased frequency of fetal and early postnatal deaths were observed in rats administered doses of 9.6 mg/kg/day (4 times* the maximum human dose on a mg/m² basis) and above.

Significant enlargement of the mammary glands in excess of the normal enlargement for pregnant rabbits was found with doses greater than or equal to 1.2 mg/kg/day (equal to the maximum human dose on a mg/m² basis). This effect occurred only in pregnant rabbits and regressed during lactation. Similar changes in the mammary glands were not observed in rats or monkeys.

There are no adequate and well-controlled studies in pregnant women. If felodipine is used during pregnancy, or if the patient becomes pregnant while taking this drug, she should be apprised of the potential hazard to the fetus, possible digital anomalies of the infant, and the potential effects of felodipine on labor and delivery, and on the mammary glands of pregnant females.

Nursing Mothers: It is not known whether this drug is secreted in human milk and because of the potential for serious adverse reactions from felodipine in the infant, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: In controlled studies in the United States and overseas approximately 3000 patients were treated with felodipine as either the extended-release or the immediate-release formulation.

The most common clinical adverse experiences reported with PLENDIL® (Felodipine, MSD) administered as monotherapy in all settings and with all dosage forms of felodipine were peripheral edema and headache. Peripheral edema was generally mild, but it was age- and dose-related and resulted in discontinuation of therapy in about 4 percent of the enrolled patients. Discontinuation of therapy due to any clinical adverse experience occurred in about 9 percent of the patients receiving PLENDIL, principally for peripheral edema, headache, or flushing.

Adverse experiences that occurred with an incidence of 1.5 percent or greater during monotherapy with PLENDIL without regard to causality are compared to placebo in the table below.

Percent of Patients with Adverse Effects in Controlled Trials of PLENDIL as Monotherapy (Incidence of discontinuations shown in parentheses)

Adverse Effect	PLENDIL % N = 730		Placebo % N = 283
Peripheral Edema	22.3	(4.2)	3.5
Headache	18.6	(2.1)	10.6
Flushing	6.4	(1.0)	1.1
Dizziness	5.8	(0.8)	3.2
Upper Respiratory Infection	5.5	(0.1)	1.1
Asthenia	4.7	(0.1)	2.8
Cough	2.9	(0.0)	0.4
Paresthesia	2.5	(0.1)	1.8
Dyspepsia	2.3	(0.0)	1.4
Chest Pain	2.1	(0.1)	1.4
Nausea	1.9	(0.8)	1.1
Muscle Cramps	1.9	(0.0)	1.1
Palpitation	1.8	(0.5)	2.5
Abdominal Pain	1.8	(0.3)	1.1
Constipation	1.6	(0.1)	1.1
Diarrhea	1.6	(0.1)	1.1
Pharyngitis	1.6	(0.0)	0.4
Rhinorrhea	1.6	(0.0)	0.0
Back Pain	1.6	(0.0)	1.1
Rash	1.5	(0.1)	1.1

*Based on patient weight of 50 kg

In the two dose response studies using PLENDIL® (Felodipine, MSD as monotherapy, the following table describes the incidenc (percent) of adverse experiences that were dose-related:

Adverse Effect	Placebo N = 121	5.0 mg N = 72	10.0 mg N = 123	20 m N = 5
Peripheral Edema	2.5	13.9	19.5	36.0
Palpitation	0.8	0.0	2.4	12.0
Headache	12.4	11.1	18.7	28.0
Flushing	0.0	2.8	8.1	20.0

In addition, adverse experiences that occurred in 0.5 up to 1.5 pe cent of patients who received PLENDIL in all controlled clinical stuc ies (listed in order of decreasing severity within each category) an serious adverse events that occurred at a lower rate or were foun during marketing experience (those lower rate events are in italics were: *Body as a Whole:* Facial edema, warm sensation; *Cardiovas cular:* Tachycardia, *myocardial infarction, hypotension, syncope angina pectoris,* arrhythmia; *Digestive:* Vomiting, dry mouth, flatu lence; *Hematologic: Anemia; Musculoskeletal:* Arthralgia, arr pain, knee pain, leg pain, foot pain, hip pain, myalgia; *Nervous/Psy chiatric:* Depression, anxiety disorders, insomnia, irritability, ne vousness, somnolence; *Respiratory:* Bronchitis, influenza sinusitis, dyspnea, epistaxis, respiratory infection, sneezing; *Skir* Contusion, erythema, urticaria; *Urogenital:* Decreased libido, im potence, urinary frequency, urinary urgency, dysuria.

Felodipine, as an immediate release formulation, has also bee studied as monotherapy in 680 patients with hypertension in U.S and overseas controlled clinical studies. Other adverse exper ences not listed above and with an incidence of 0.5 percent c greater include: *Body as a Whole:* Fatigue; *Digestive:* Gastrointest nal pain; *Musculoskeletal:* Arthritis, local weakness, neck pair shoulder pain, ankle pain; *Nervous/Psychiatric:* Tremor; *Respira tory:* Rhinitis; *Skin:* Hyperhidrosis, pruritus; *Special Senses:* Blurre vision, tinnitus; *Urogenital:* Nocturia.

Gingival Hyperplasia: Gingival hyperplasia, usually mild, occurre in <0.5 percent of patients in controlled studies. This condition ma be avoided or may regress with improved dental hygiene. (Se PRECAUTIONS, *Information for Patients.*)

Clinical Laboratory Test Findings: ***Serum Electrolytes:*** No sig nificant effects on serum electrolytes were observed during short and long-term therapy (see CLINICAL PHARMACOLOGY, *Rena Endocrine Effects*).

Serum Glucose: No significant effects on fasting serum glucos were observed in patients treated with PLENDIL in the U.S. con trolled study.

Liver Enzymes: One of two episodes of elevated serum trans aminases decreased once drug was discontinued in clinical stuc ies; no follow-up was available for the other patient.

OVERDOSAGE: Oral doses of 240 mg/kg and 264 mg/kg in mal and female mice, respectively, and 2390 mg/kg and 2250 mg/kg i male and female rats, respectively, caused significant lethality.

In a suicide attempt, one patient took 150 mg felodipine tc gether with 15 tablets each of atenolol and spironolactone and 2 tablets of nitrazepam. The patient's blood pressure and heart rat were normal on admission to hospital; he subsequently recovere without significant sequelae.

Overdosage might be expected to cause excessive peripher vasodilation with marked hypotension and possibly bradycardia.

If severe hypotension occurs, symptomatic treatment shoul be instituted. The patient should be placed supine with the legs ele vated. The administration of intravenous fluids may be useful to trea hypotension due to overdosage with calcium antagonists. In case c accompanying bradycardia, atropine (0.5-1 mg) should be admin istered intravenously. Sympathomimetic drugs may also be given the physician feels they are warranted.

It has not been established whether felodipine can be remove from the circulation by hemodialysis.

DOSAGE AND ADMINISTRATION: The recommended initial dos is 5 mg once a day. Therapy should be adjusted individually accord ing to patient response, generally at intervals of not less than tw weeks. The usual dosage range is 5-10 mg once daily. The maxi mum recommended daily dose is 20 mg once a day. That dose i clinical trials showed an increased blood pressure response but large increase in the rate of peripheral edema and other vasodila tory adverse events (see ADVERSE REACTIONS). Modification c the recommended dosage is usually not required in patients wit renal impairment.

PLENDIL should be swallowed whole and not crushed c chewed.

Use in the Elderly or Patients with Impaired Liver Function: Pa tients over 65 years of age or patients with impaired liver functior because they may develop higher plasma concentrations of felodi pine, should have their blood pressure monitored closely durin dosage adjustment (see PRECAUTIONS). In general, doses abov 10 mg should not be considered in these patients.

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Evaluation of Coronary Artery Disease in the Hurler Syndrome by Angiography

Elizabeth A. Braunlin, MD, PhD, David W. Hunter, MD, William Krivit, MD, PhD, Barbara A. Burke, MD, Peter S. Hesslein, MD, Priscilla T. Porter, MD, and Chester B. Whitley, PhD, MD

Hurler syndrome (mucopolysaccharidosis type I-H) is an inherited lysosomal storage disease characterized by the widespread accumulation of mucopolysaccharide in tissues throughout the body.[1] Although severe coronary artery luminal narrowing has been documented by postmortem examination of the heart of patients with Hurler syndrome,[2] the only reported study in which coronary angiography was performed stated that the coronary arteries appeared normal.[3] As part of an ongoing protocol at our institution, selective coronary angiography was performed in children with Hurler syndrome before bone marrow transplantation. The subsequent availability of postmortem material from 3 such patients has allowed us to perform a retrospective analysis of the usefulness of selective coronary angiography in detecting the presence of coronary artery disease in patients with the Hurler syndrome.

Seven children (3 boys and 4 girls), 0.9 to 3.4 years of age (mean 1.9), were diagnosed with Hurler syndrome by the presence of the typical clinical stigmata, elevated levels of urinary glycosaminoglycans and complete deficiency of leukocyte α-L-iduronidase enzyme activity. At cardiac catheterization, each child was given heparin (100 U/kg) after introduction of the arterial cannula. Multiple selective hand injections of 1 to 7 ml of nonionic contrast were performed into the right and left coronary ostia using 4 or 5Fr JB1 catheters, specially designed to accommodate each patient's small size. In 2 patients, ostial cannulation was not achieved and either aortic cusp or root injection was performed. Standard angulated views (long axial oblique cranial, right anterior oblique caudal) were the primary views used to visualize the coronary arteries.

Each angiogram was reviewed without knowledge of the outcome of the case by a cardiovascular radiologist (DWH) for the presence of luminal irregularities or discrete stenoses and for paucity of third-order branching. Angiograms were defined (1) normal if no abnormality was identified, or (2) abnormal if stenoses or irregularities of the epicardial coronary vessels or pruning of third-order coronary branches was present. A total of 23 selective coronary arteriograms, 3 aortic cusp injections and 1 aortic root injection were available for review from the 7 patients.

Postmortem material was available in 3 patients. In each instance, inspection of coronary ostia as well as the distribution and gross appearance of the coronary arteries was made. Histopathologic sections from left main, left anterior descending, circumflex and right coronary arteries were obtained, fixed in 10% formaldehyde and processed in a routine manner. In addition to hematoxylin-eosin, histopathologic sections were stained with colloidal iron, periodic acid Schiff, trichome (azocarmine) and elastic van Gieson stains using standard techniques.

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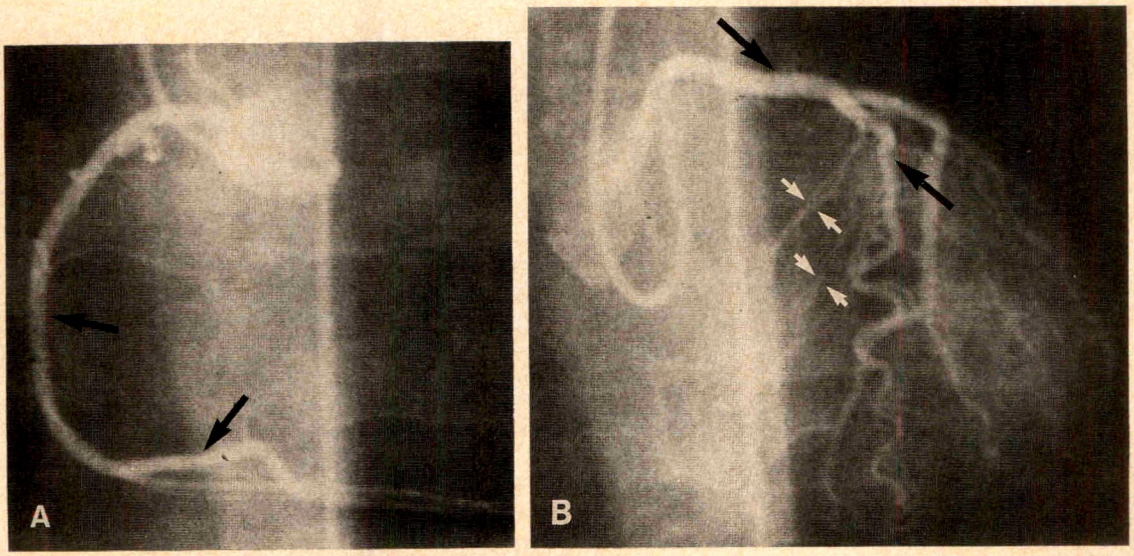


FIGURE 1. ***A*, normal right coronary arteriogram, right anterior oblique projection, from a 15-month old male infant with Hurler syndrome before bone marrow transplantation. *B*, normal left coronary arteriogram, right anterior oblique projection, from same patient. Note the absence of luminal irregularities or stenoses within the large epicardial arteries (*A and B, black arrows*) and the abundance of third-order branches (*B, white arrows*).**

Coronary arteries were considered normal by angiography in 2 of the 7 patients (Figure 1, A and B). Ventricular tachycardia and cardiac arrest occurred immediately after completion of catheterization in 1 of these 2 patients, a 15-month old boy. He was unable to be resuscitated. Histopathologic examination revealed moderate to severe diffuse luminal narrowing of all extramural coronary arteries due to the presence of so-called Hurler cells, and excessive amounts of collagen and glycosaminoglycans (Figure 2, A and B). There was no histologic evidence for either recent or old myocardial ischemia or necrosis. The resting electrocardiogram before catheterization was normal, as was left ventricular size and function on 2-dimensional echocardiogram.

Coronary arteries were considered abnormal in the remaining 5 children in whom either mild irregularities of the left main coronary artery or its first-order branches, or marked paucity of third-order branching of either right or left coronary artery were noted (Figure 3A). Two children died in this group: patient 1 from pulmonary complications of graft versus host disease which occurred 4 months after successful bone marrow transplantation and angiography had been performed, and patient 2 from apparent sepsis and graft versus host disease 13 months after angiography and successful bone marrow transplantation. Histopathologic examination in both instances revealed moderate to severe diffuse luminal narrowing of extramural coronary arteries due to deposition of mucopolysaccharides and collagen (Figure 3B). Histologic evaluation of the intramyocardial coronary arteries was normal. The myocardium was normal in patient 2 and (except for a small section) unavailable for review in patient 3. Resting electrocardiogram and 2-dimensional echocardiogram before catheterization were normal in patient 2 and showed only mild left ventricular hypertrophy in patient 3.

The 4 remaining children are alive 2.3 to 4.5 years (mean 3.2) after successful bone marrow transplantation. Repeat coronary angiography has not been performed.

Diffuse infiltration within the intima of extramural coronary arteries by clear cells (the so-called Hurler

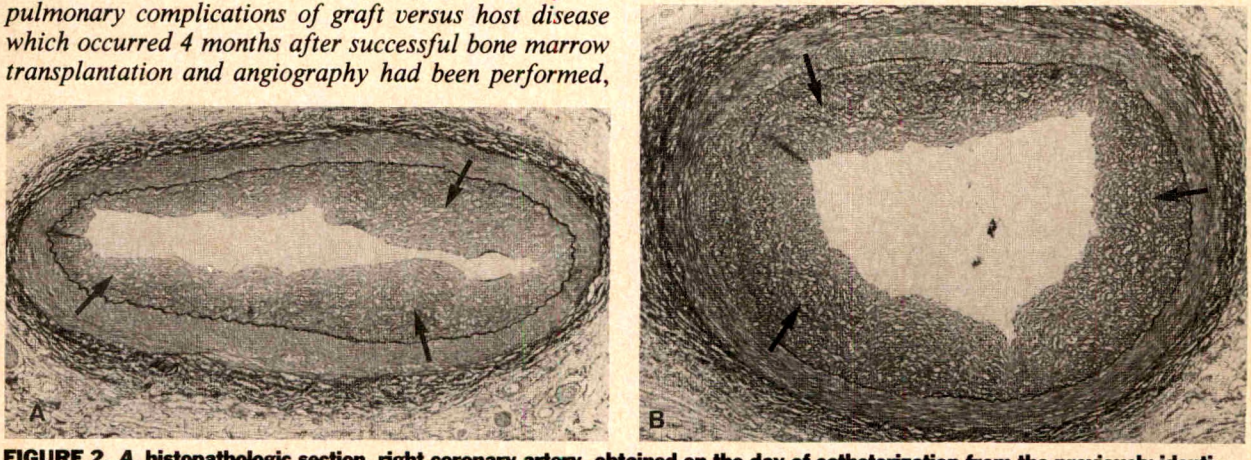


FIGURE 2. *A*, histopathologic section, right coronary artery, obtained on the day of catheterization from the previously identified infant in Figure 1. *B*, histopathologic section, left coronary artery from the same patient. Note the concentric luminal narrowing *(A and B, black arrows)* from myointimal proliferation and diffuse infiltration of the intima by mucopolysaccharides, Hurler cells and fibrosis. (Elastic van Gieson stain, final magnification × 100, both *A and B* reduced by 52%.)

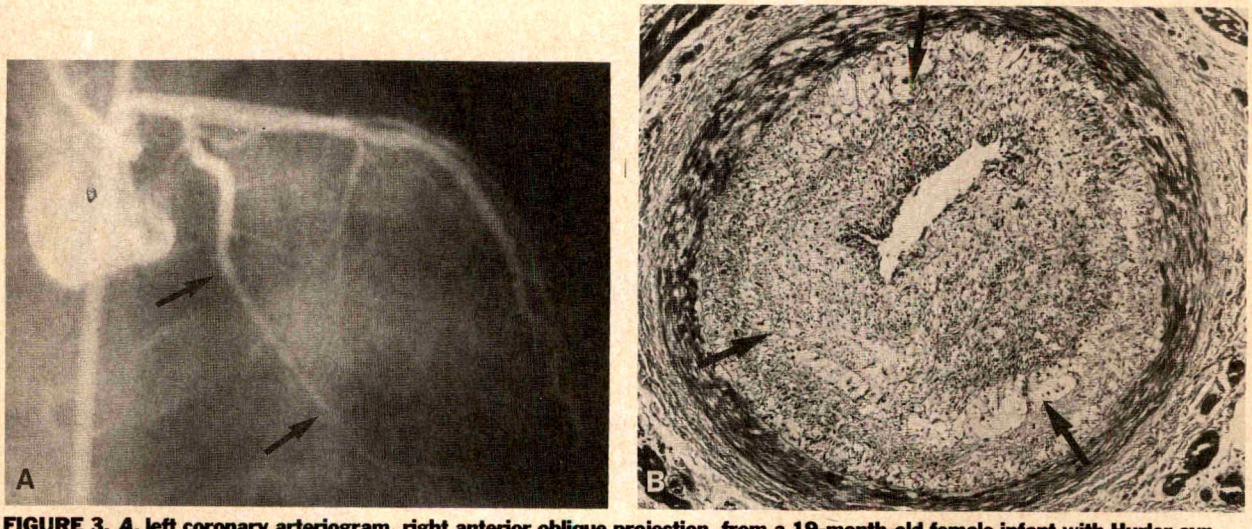


FIGURE 3. *A*, left coronary arteriogram, right anterior oblique projection, from a 19-month-old female infant with Hurler syndrome before bone marrow transplantation. Note the rapid tapering of the first obtuse marginal branch of the left main coronary artery *(black arrows)* and the paucity of third-order branching (compared with Figure 1B). *B*, histopathologic section, extramural coronary artery from same patient, obtained 13 months after successful bone marrow transplantation. Note severe diffuse myointimal proliferation *(black arrows)* with near total luminal occlusion. (Azocarmine stain, final magnification × 126, reduced by 60%.)

cells), acid mucopolysaccharide and collagen is a characteristic feature of the histopathology of the Hurler syndrome.[2,4] Although coronary angiography has been performed infrequently in these children, it has been reported to be normal.[3] The striking discrepancy between the angiographic and corresponding pathologic appearances of the large extramural coronary arteries reported in our study provides strong evidence that coronary angiography underestimates the severity of the diffuse coronary artery disease present in children with the Hurler syndrome. In the 3 patients in whom both angiographic and pathologic data were available, the angiographic abnormalities were either undetectable (patient 1), discrete and mild (patients 2 and 3), or identified primarily in small third-order branches rather than the large extramural arteries (patient 3). By contrast, the pathologic findings in each of the 3 patients were moderate to severe, and confined to the large epicardial coronary vessels.

The inability of selective coronary angiography to detect diffuse coronary artery disease is not unique to the Hurler syndrome, having previously been reported in other processes such as the chronic vascular rejection seen in cardiac transplant recipients.[5] Although it is possible that coronary artery disease developed in the interim between angiography and postmortem examination in 2 of the patients reported here, no interim occurred in the first patient in whom the angiographic and pathologic findings were also discrepant.

Accurate assessment of coronary artery disease in the mucopolysaccharidoses is important not only for clinical management of the patient, but also to determine if bone marrow transplantation is able to halt or reverse the deposition of storage material that occurs in this group of diseases. Significant coronary artery disease was still present in the 2 children reported here who survived 4 and 13 months after successful engraftment of bone marrow and may have played a role in the sudden death of 1 of these children. Whether sufficient regression may occur over a longer time period to justify bone marrow transplantation is unknown. There have been no late deaths from cardiac or any causes in the remaining children in this study. Long-term follow-up of these youngsters will be especially important to determine if the natural history of the disease has been favorably influenced by bone marrow transplantation.

In summary, we have found that severe diffuse coronary artery disease can occur early in the course of the Hurler syndrome, that selective coronary angiography underestimates the extent of the disease, and that significant coronary artery disease is present as long as 13 months after successful bone marrow transplantation.

Acknowledgment: We gratefully acknowledge the contribution of James C. Harkin, MD, to this work.

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Frequency of Isolated Panic Attacks and Panic Disorder in Patients with the Mitral Valve Prolapse Syndrome

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Panic disorder is a specific form of anxiety disorder that shares several clinical features with the mitral valve prolapse (MVP) syndrome.[1,2] Studies attempting to define the relation between these disorders have produced conflicting results.[3–5] This study prospectively assesses the frequency of isolated panic attacks and panic disorder in patients with the MVP syndrome.

Consecutive outpatient subjects with chest pain, palpitations, presyncope or syncope, or effort intolerance/dyspnea were considered eligible for the study. Patients with underlying organic heart disease (other than MVP) based on medical history, physical examination, chest x-ray, resting and 24-hour ambulatory (for those with palpitations, or presyncope or syncope) electrocardiograms, echocardiogram (M-mode, 2-dimensional, Doppler and color flow) and treadmill exercise testing with thallium 201 scintigraphy (in those with chest pain) were excluded from the study. Patients previously diagnosed with MVP, and those who previously received a discrete psychiatric diagnosis by a psychiatrist or psychologist were also excluded.

The interviewing physician needed to commit in writing as to the presence or absence of isolated panic attacks or panic disorder before performing the physical examination or obtaining/reviewing laboratory tests. Echocardiography was performed in accordance with American Society of Echocardiography guidelines using a Hewlett-Packard Sonos 1000 ultrasonograph and 2.25 MHz transducer. MVP was diagnosed in accordance with the criteria of Perloff et al.[1] The MVP syndrome was de-

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TABLE I Criteria for Panic Attacks and Panic Disorder

Panic attacks
- Discrete periods of intense fear or discomfort associated with ≥ 4 of following:
  - Shortness of breath or smothering sensations
  - Palpitations; acceleration of heart rate
  - Chest pain or discomfort
  - Sweating
  - Faintness, dizziness, lightheadedness or unsteady feelings
  - Nausea or abdominal distress
  - Depersonalization or derealization
  - Numbness or tingling sensations
  - Flushes, hot flashes or chills
  - Trembling or shaking
  - Fear of dying
  - Fear of going crazy or doing something uncontrolled
- Not caused by any organic factor or circumscribed phobic stimulus
- Isolated panic attacks are those occurring with insufficient frequency to diagnose panic disorder

Panic disorder
- ≥ 3 panic attacks within a 3-week period

TABLE II Patient Characteristics and Clinical Features

Patient Characteristics and Clinical Features	MVP Group (%)	Control Group (%)	p Value
Pts.	44	55	—
Women	34 (77)	41 (74)	NS
Men	10 (23)	14 (26)	NS
Mean age (yr)	33 ± 8	30 ± 10	NS
Palpitations	28 (64)	36 (60)	NS
Chest pain/discomfort	20 (45)	27 (49)	NS
Presyncope/syncope	10 (23)	14 (25)	NS
Dyspnea, effort intolerance	8 (18)	12 (22)	NS
Isolated panic attacks	10 (23)	14 (25)	NS
Panic disorder	9 (20)	12 (22)	NS
Isolated panic attacks or panic disorder	19 (43)	26 (47)	NS

MVP = mitral valve prolapse syndrome; NS = not significant.

fined as clinical and echocardiographic MVP associated with otherwise unexplained chest pain, palpitations, syncope or effort intolerance (dyspnea), or a combination.[1] Panic attacks and panic disorder were defined in accordance with DSM-III-R[2] criteria (Table I).

Initially, 227 patients were considered for entry in the study. An organic etiology for symptoms other than MVP was identified in 133 patients. These patients were excluded. Thus, 94 patients entered the study. Of these patients, 44 had clinical and echocardiographic criteria for MVP (MVP group). Fifty patients had a normal cardiovascular examination and no evidence of organic heart disease on noninvasive cardiac tests (control group). Table II summarizes patient characteristics in these 2 groups.

Table II shows the frequency of isolated panic attacks or panic disorder, or both, in the MVP and control groups. There was no significant difference in the frequency of any form of panic between the 2 groups. The chi-square test was used to determine if the frequency of variables in the MVP group differed from those in the control group.

In an essay on soldier's heart, DaCosta's syndrome, and neurocirculatory asthenia and the effort syndrome, Wooley[6] persuasively draws a link between functional cardiac disorders and the MVP syndrome. To this end, several investigators have explored the relation between MVP and panic disorder.[3–5] In studies of patients with panic disorder, the reported frequency of MVP ranges from 7 to 34%, and does not exceed that of normal control subjects or that expected based on age and gender distribution.[3–5] The present study focused on the frequency of isolated panic attacks and panic disorder in patients with the MVP syndrome.

TABLE III Reported Frequency of Panic Manifestations in Patients with Mitral Valve Prolapse—Controlled Studies

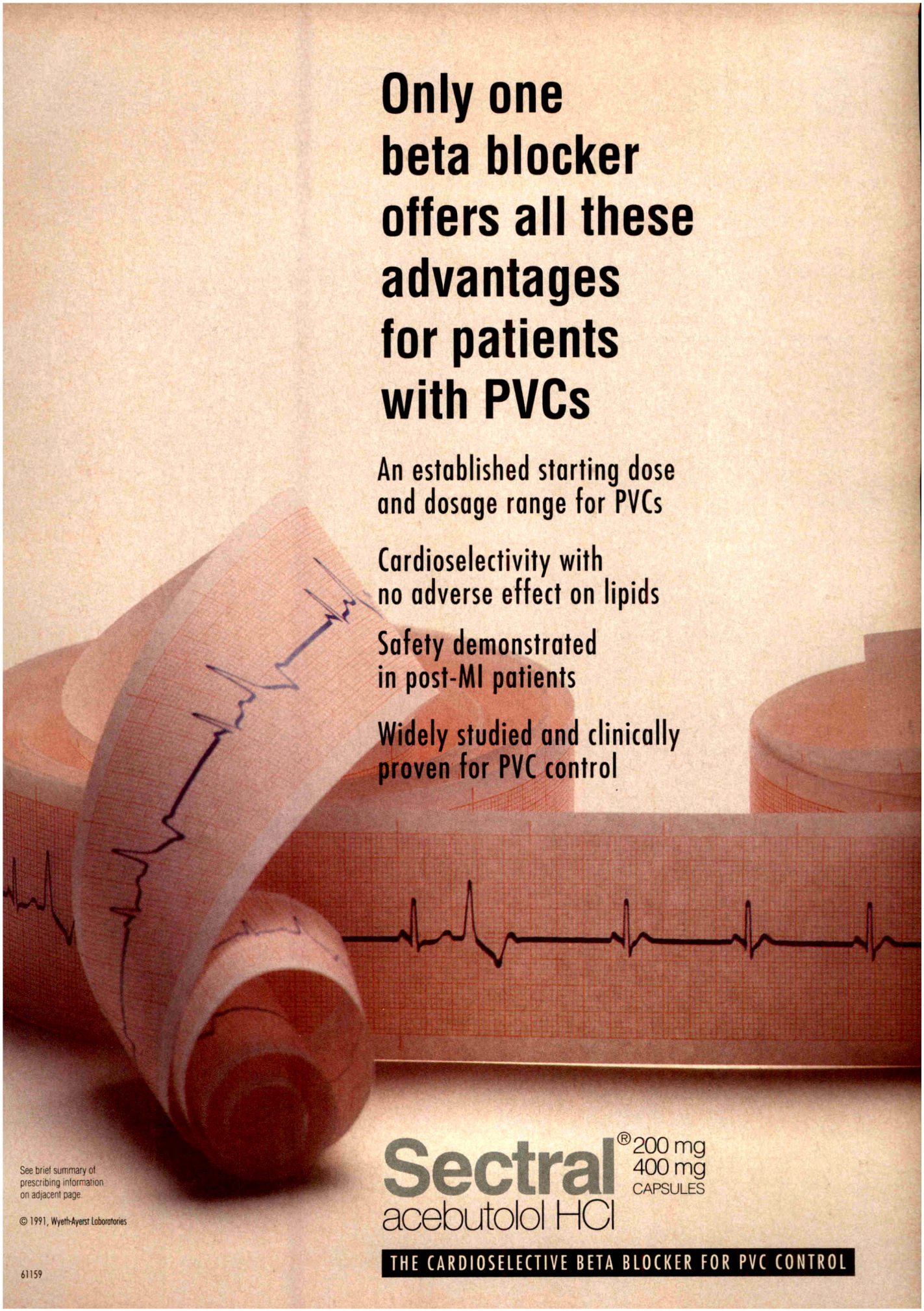
	Frequency of Panic Manifestations (%)					
	MVP Group			Control Group		
Investigator	n	Isolated Panic Attacks	Panic Disorder	n	Isolated Panic Attacks	Panic Disorder
Kane[3–5]	65	25	8	33*	14	6
				22†	5	5
Hartman[3–5]	141	21	16	70‡	5	5
Hickey[3–5]	103	—	3	67*	10	3
Devereaux[3–5]	88	16	14	172§	8	2
Mazza[3–5]	48	—	0	60†	3	2
Present study	44	23	20	55	25	22

*With nonspecific cardiac symptoms; †asymptomatic normal control subjects; ‡family members; §first-degree relatives and normal unmatched control subjects. MVP = mitral valve prolapse.

Controlled studies assessing the frequency of panic attacks and panic disorder in patients with the MVP syndrome have produced conflicting results.[3–5] The results of these studies are summarized in Table III together with the results of the present study.[3–5] The observed disparity may be attributable in part to differences in the diagnostic criteria for MVP and panic disorder, but is primarily due to variations among the control groups.[3–5] Because of the overlap in clinical manifestations, it is predictable that panic manifestations will occur with higher frequency in patients with the MVP syndrome than in normal (presumably asymptomatic) control subjects. Conversely, it is not surprising that control groups of "normal" patients with cardiovascular symptoms would demonstrate a high frequency of isolated panic attacks and panic disorder owing to unavoidable ascertainment bias. The possibility of ascertainment bias is not eliminated in the present study; however, the design of the study ensures equal bias in the MVP and control groups.

This study shows that there is a high rate of co-occurrence of the MVP syndrome and panic manifestations. The results do not demonstrate that isolated panic attacks and panic disorder occur with disproportionately high frequency in patients with the MVP syndrome.

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CONTRAINDICATIONS: SECTRAL is contraindicated in: 1) persistently severe bradycardia; 2) second- and third-degree heart block; 3) overt cardiac failure; 4) cardiogenic shock. (See WARNINGS)

WARNINGS: Cardiac Failure: Sympathetic stimulation may be essential for support of circulation in patients with diminished myocardial contractility and inhibition by β-adrenergic receptor blockade may precipitate more severe failure. Although β-blockers should be avoided in overt cardiac failure, SECTRAL can be used cautiously when heart failure is controlled with digitalis and/or diuretics. Digitalis and SECTRAL impair AV conduction. Withdraw SECTRAL if cardiac failure persists.

In Patients Without a History of Cardiac Failure: In patients with aortic or mitral valve disease or compromised left ventricular function, continued depression of the myocardium with β-blockers over time may lead to cardiac failure. Digitalize patients at first signs of failure, and/or give a diuretic and observe closely. Withdraw SECTRAL if cardiac failure persists.

Exacerbation of Ischemic Heart Disease Following Abrupt Withdrawal: Abrupt discontinuation of some β-blockers in coronary artery disease patients may exacerbate angina; in some cases, myocardial infarction and death have been reported. Caution such patients against interruption of therapy without a physician's advice. Even in the absence of overt ischemic heart disease, withdraw SECTRAL gradually over a period of about two weeks; observe carefully and advise patients to minimize physical activity during this time. (If desired, patients may be transferred directly to comparable doses of an alternative β-blocker without interruption of β-blocking therapy.) If exacerbation of angina occurs, restart full-dose anti-anginal therapy immediately and hospitalize patient until stabilized.

Peripheral Vascular Disease: β-antagonists reduce cardiac output and can precipitate/aggravate arterial insufficiency in patients with peripheral or mesenteric vascular disease. Exercise caution and observe such patients closely for progression of arterial obstruction.

Bronchospastic Diseases: Patients with Bronchospastic Disease Should, in General, Not Receive a β-Blocker. Because of its relative β_1-selectivity, low doses of SECTRAL may be used cautiously in such patients who do not respond to, or cannot tolerate, alternative treatment. Since β_1-selectivity is not absolute and is dose-dependent, use lowest possible dose of SECTRAL initially, preferably in divided doses. Make bronchodilator, e.g., theophylline, or a β_2-stimulant, available in advance with instructions for use.

Anesthesia and Major Surgery: The necessity/desirability of withdrawing β-blockers prior to major surgery is controversial; the heart's impaired ability to respond to β-adrenergically mediated reflex stimuli may enhance the risk of excessive myocardial depression during general anesthesia. Difficulty in restarting and maintaining the heartbeat also has been reported with beta-blockers. If treatment is continued, take special care when using anesthetics that depress the myocardium; use lowest possible SECTRAL dose. SECTRAL, like other β-blockers, is a competitive inhibitor of β-receptor agonists, so its effects can be reversed by cautious administration of such agents (e.g., dobutamine or isoproterenol). Symptoms of excessive vagal tone (e.g., profound bradycardia, hypotension) may be corrected with atropine.

Diabetes and Hypoglycemia: β-blockers may potentiate insulin-induced hypoglycemia and mask some symptoms such as tachycardia; dizziness and sweating are usually not significantly affected. Warn diabetics of possible masked hypoglycemia.

Thyrotoxicosis: β-adrenergic blockade may mask some clinical signs (tachycardia) of hyperthyroidism. Abrupt withdrawal of SECTRAL may precipitate a thyroid storm in patients suspected of developing thyrotoxicosis.

PRECAUTIONS: Impaired Renal or Hepatic Function: While there are no U.S. studies, foreign published experience shows that acebutolol has been used successfully in chronic renal insufficiency. Acebutolol is excreted via the G.I. tract, but the active metabolite, diacetolol, is eliminated mainly by the kidney. A linear relationship exists between renal clearance of diacetolol and creatinine clearance (Cl_{cr}); reduce daily dose of acebutolol by 50% when Cl_{cr} is less than 50 mL/min and by 75% when it is less than 25 mL/min. Use cautiously in patients with impaired hepatic function.

SECTRAL has been used successfully and without problems in elderly patients in U.S. clinical trials without specific dosage adjustment. However, in the elderly, lower maintenance doses may be required because bioavailability of SECTRAL and its metabolite are approximately doubled.

Information for Patients: Warn patients, especially those with evidence of coronary artery disease, against interruption or discontinuation of SECTRAL without physician supervision. Although cardiac failure rarely occurs in properly selected patients, advise patients to consult a physician if signs or symptoms suggestive of impending CHF, or unexplained respiratory symptoms, develop.

Warn patients of possible severe hypertensive reactions from concomitant use of α-adrenergic stimulants, e.g., nasal decongestants used in OTC cold medicines and nasal drops.

Clinical Laboratory Findings: SECTRAL, like other β-blockers has been associated with development of antinuclear antibodies (ANA). In prospective clinical trials, patients receiving SECTRAL had a dose-dependent increase in the development of positive ANA titers. Symptoms related to this laboratory abnormality were infrequent. Symptoms and ANA titers were reversible upon discontinuation of SECTRAL.

Drug Interactions: Catecholamine-depleting drugs may have additive effects when given with β-blockers. Observe patients treated with both agents closely for evidence of marked bradycardia or hypotension which may present as vertigo, syncope/presyncope, or orthostatic changes in blood pressure without compensatory tachycardia. Exaggerated hypertensive responses have been reported from use of β-adrenergic antagonists with α-adrenergic stimulants, including those in OTC cold remedies and vasoconstrictive nasal drops. Nonsteroidal anti-inflammatory drugs may blunt antihypertensive effects of beta-blockers.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Chronic oral toxicity studies in rats and mice, at doses 15 times the maximum recommended (60 kg) human dose, did not indicate carcinogenic potential for SECTRAL. Diacetolol, the major metabolite in man, was without carcinogenic potential in rats at doses up to 1800 mg/kg/d. SECTRAL and diacetolol also had no mutagenic potential in the Ames Test. No significant impact on reproductive performance or fertility was found in rats following SECTRAL or diacetolol doses of up to 240 or 1000 mg/kg/d, respectively.

Pregnancy: *Teratogenic Effects:* Pregnancy Category B: No teratogenic effects were seen in rat or rabbit reproduction studies utilizing SECTRAL doses that were, respectively, approximately 31.5 and 6.8 times the maximum recommended human dose. At this dose in the rabbit, slight fetal growth retardation was noted; this was considered to be a result of maternal toxicity (evidenced by reduced food intake, lowered rate of body weight gain, mortality). Diacetolol studies (doses up to 450 mg/kg/d in rabbits and up to 1800 mg/kg/d in rats) showed no evidence of fetal harm other than a significant elevation in postimplantation loss with 450 mg/kg/d, a level at which food consumption and body weight gain were reduced in rabbit dams; there was a nonstatistically significant increase in incidence of bilateral cataract in rat fetuses from dams treated with 1800 mg/kg/d. There are no adequate and well-controlled trials in pregnant women; SECTRAL should be used during pregnancy only if potential benefit justifies risk to the fetus.

Nonteratogenic Effects: Human studies indicate that acebutolol and diacetolol cross the placenta. Neonates of mothers who received acebutolol during pregnancy have reduced birth weight, decreased blood pressure, and decreased heart rate.

Labor and Delivery: Effect on labor and delivery in pregnant women is unknown. Animal studies have shown no effect of SECTRAL on the usual course of labor and delivery.

Nursing Mothers: Acebutolol and diacetolol appear in breast milk (milk: plasma ratio of 7.1 and 12.2, respectively). Use in nursing mothers is not recommended.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: SECTRAL is well tolerated in properly selected patients. Most adverse effects have been mild, not required therapy discontinuation, and tended to decrease as treatment duration increases.

The incidence of treatment-related side effects (volunteered and elicited) derived from U.S. controlled clinical trials in patients with hypertension, angina and arrhythmia follows. Numbers represent percentage incidence for SECTRAL (N =1002) versus placebo (N=314), respectively.

Cardiovascular: Chest pain 2%, 1% Edema 2%, 1%. *CNS:* Depression 2%,1%; Dizziness 6%, 2%; Fatigue 11%, 4%; Headache 6%, 4%; Insomnia 3%, 1%; Abnormal dreams 2%, 1%. *Dermatologic:* Rash 2%, 1%. *Gastrointestinal:* Constipation 4%, 0%; Diarrhea 4%, 1%; Dyspepsia 4%, 1%; Flatulence 3%, 1%; Nausea 4%, 0%. *Genitourinary:* Micturition (frequency) 3%, <1%. *Musculoskeletal:* Arthralgia 2%, 2%; Myalgia 2%, 0%. *Respiratory:* Cough 1%, 0%; Dyspnea 4%, 2%; Rhinitis 2%, <1%. *Special Senses:* Abnormal Vision 2%, 0%.

The following selected (potentially important) side effects were seen in up to 2% of SECTRAL patients: *Cardiovascular:* hypotension, bradycardia, heart failure. *CNS:* anxiety hyper/hypoesthesia, impotence. *Skin:* pruritus. *Gastrointestinal:* vomitting, abdominal pain. *Genitourinary:* dysuria, nocturia. *Liver and Biliary:* small number of reported cases of liver abnormalities (increased SGOT, SGPT, LDH). In some cases, increased bilirubin or alkaline phosphatase, fever, malaise, dark urine, anorexia, nausea, headache, and/or other symptoms have been reported. In some cases, symptoms and signs were confirmed by rechallenge. Abnormalities were reversible upon drug cessation. *Musculoskeletal:* back and joint pain. *Respiratory:* pharyngitis, wheezing. *Special Senses:* conjunctivitis, dry eye, eye pain. *Autoimmune:* extremely rare reports of systemic lupus erythematosis.

Incidence of drug-related adverse effects (volunteered and solicited) based on SECTRAL dose is shown below. (Data from 266 hypertensive patients treated for 3 months on a constant dose.)

Body System	400 mg/day (N = 132)	800 mg/day (N = 63)	1200 mg/day (N = 71)
Cardiovascular	5%	2%	1%
Gastrointestinal	3%	3%	7%
Musculoskeletal	2%	3%	4%
Central Nervous System	9%	13%	17%
Respiratory	1%	5%	6%
Skin	1%	2%	1%
Special Senses	2%	2%	6%
Genitourinary	2%	3%	1%

Potential Adverse Effects: Certain adverse effects not listed above have been reported with other β-blocking agents and should be considered as potential adverse effects of SECTRAL.

CNS: Reversible mental depression progressing to catatonia, an acute syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.

Cardiovascular: Intensification of AV block (see CONTRAINDICATIONS). *Allergic:* Erythematous rash, fever with aching and sore throat, laryngospasm, respiratory distress.

Hematologic: Agranulocytosis, nonthrombocytopenic and thrombocytopenic purpura.

Gastrointestinal: Mesenteric arterial thrombosis, ischemic colitis.

Miscellaneous: Reversible alopecia, Peyronie's disease. The oculomucocutaneous syndrome associated with practolol has not been reported with SECTRAL.

Keep at room temperature, Approximately 25°C (77°F).

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Atypical Systolic Clicks Produced by Prolapsing Mitral Valve Masses

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Mid- or late-systolic clicks were originally thought to be extracardiac in origin.[1] It was not until the 1960s that these clicks were demonstrated by angiography to be associated with late systolic prolapse of the mitral valve and mitral regurgitation.[2] This was subsequently confirmed by intracardiac phonocardiographic recording of clicks and late systolic murmurs in the left (but not the right) atrium.[3] Since that time, occasional cases of mid- and late-systolic sounds have been described in the absence of mitral valve prolapse. These include a left ventricular tumor prolapsing into the left atrium,[4] a right ventricular tumor prolapsing across the pulmonic valve,[5] right atrial myxomas "plopping" in and out of the right ventricle,[6] severe aortic regurgitation[7] and prolapse of the tricuspid valve.[8] The present report reviews a previous case we described of a midsystolic click produced by a prolapsing prosthetic mitral valve vegetation[9] and describes 2 additional cases of atypical midsystolic clicks associated with prolapsing mitral valve masses. We propose that the mechanism of sound production was the same in all 3 cases and was associated with abrupt movement of a mitral leaflet toward the left ventricle during "disengagement" of the mass from the mitral valve apparatus, and prolapse into the left atrium.

The clinical characteristics of the three patients with atypical systolic clicks and prolapsing mitral valve masses are shown in Table I. The heavily calcified ruptured chorda in patient 1 is shown to prolapse into the left atrium during systole (Figure 1). The midsystolic sound occurs intermittently and only at the onset of prolapse of the chorda (Figure 2). In patient 2, a vegetation attached to the anterior leaflet of the native mitral valve prolapses into the left atrium during systole (Figure 3). The systolic sound is only present on beats when the mass prolapses (Figure 4). In patient 3, the prolapsing vegetation was attached to a prosthetic mitral valve (Figure 5). This mass "engages" the mitral valve (on the second beat of Figure 6), but only produces a sound on beats where disengagement and prolapse of the mass occurs.

These cases demonstrate midsystolic sounds produced by prolapsing mitral valve masses on 3 different but abnormal mitral valves. In the first patient, the sound was produced by a heavily calcified ruptured chorda attached to a native, rheumatic, previously infected, mitral valve; in the second, by a vegetation on a native rheumatic mitral valve; and in the third, by a vegetation on a bioprosthetic mitral valve. In each case, the sound produced was clearly caused by the prolapsing mass and was not simply a result of mitral valve prolapse. In all 3 patients, the sound was intermittent and only present on beats when the mass prolapsed. In patients 1 and 2, the timing of prolapse varied from beat to beat, and the timing of the systolic sound varied accordingly. In patient 3, the sound did not occur after the mass embolized to the femoral artery.

Despite the differences in underlying mitral valve pathology and anatomy among the 3 cases, the sounds produced were similar. In each case, the systolic sounds were as loud as or louder than the first heart sound. They were high frequency and heard throughout the precordium. The sounds differed from the midsystolic click of mitral valve prolapse, because they were more coarse and of greater duration.

Because these sounds were similar, a unique opportunity to assess the mechanism of sound production presented itself. The sounds could be produced by the mass striking a cardiac structure — either the left atrial wall or the mitral valve cusps (Figure 7A). Both systolic and diastolic tumor sounds or "plops" due to masses striking chamber walls have been described.[6,10,11] Furthermore, the striking of a tumor against the mitral valve cusps has been suggested as 1 cause of the increased first heart sound in cases of left atrial myxomas.[12] The masses in the present patients did not strike the left atrial walls during prolapse. The masses did strike the mitral valve leaflets as they prolapsed. However, the masses also struck the leaflets on beats without mass prolapse (e.g., beat 2 in Figure 6), and no click occurred on those beats.

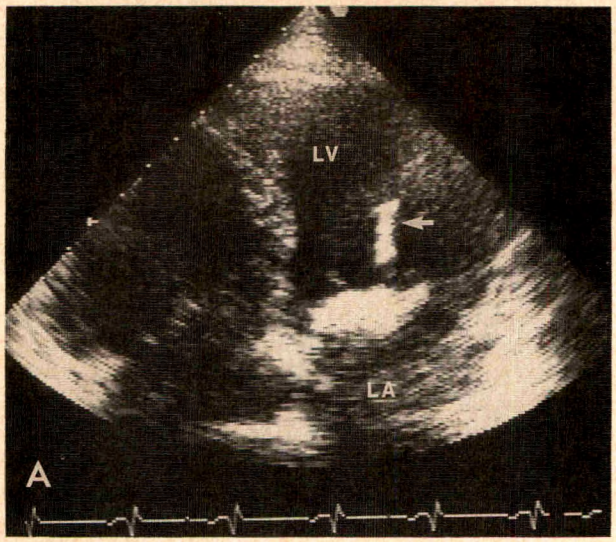
Another potential mechanism of sound production is abrupt tensing of the chordae tendinae or mitral valve apparatus during prolapse. The clicks of mitral valve

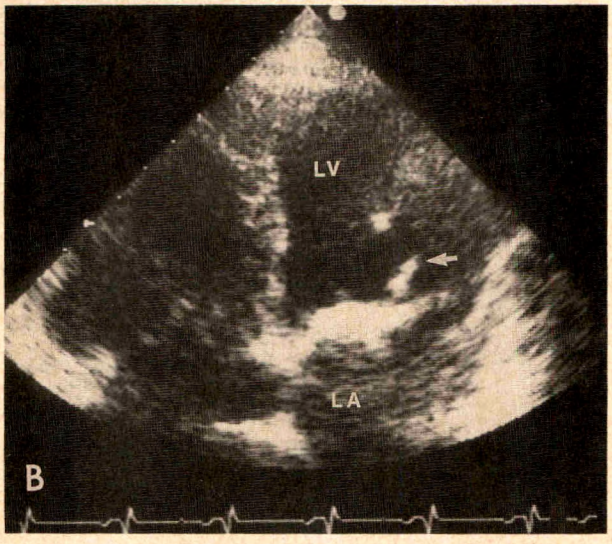
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TABLE I Clinical Characteristics of Patients with Systolic Click and Mitral Valve Mass

Pt. No.	Age (yr) & Sex	Underlying MV Disease	Presenting Complaint	MV Pathology	Diagnosis	MV Mass	Associated Organism
1	68F	RHD Endocarditis	Asymptomatic	MS (moderate) MR (severe)	Ruptured chorda	Ruptured chorda	H. parainfluenza (previous infection)
2	38F	RHD	Fever/chills joint pain	MR (mild)	Native endocarditis	Ant. leaflet MV veg.	S. viridans
3	77F	Porcine MV replacement	Fever fatigue	MR (mild)	Prosthetic endocarditis	Prosthetic MV veg.	S. viridans

Ant. = anterior; H. = hemophilus; MR = mitral regurgitation; MS = mitral stenosis; MV = mitral valve; RHD = rheumatic heart disease; S. = streptococcus; veg. = vegetation.





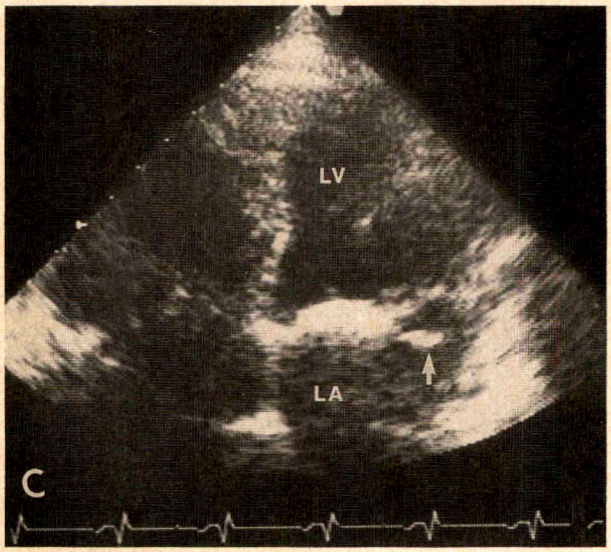


FIGURE 1. Apical 4-chamber view of 2-dimensional echocardiogram at end-diastole *(A)*, early systole *(B)* and mid-systole *(C)* in case 1. At end-diastole, heavily calcified chorda *(arrow)* in left ventricle (LV) extends from calcified mitral valve toward papillary muscle. In early systole, this chorda moves toward mitral valve. In mid-systole, chorda is seen in left atrium (LA).

prolapse may be related to this mechanism.[1] Tensing of the chordae, or the "chordal snap" (Figure 7B), is probably not the operative mechanism in these cases, because in 1 case (patient 3), the mitral valve was bioprosthetic and without chordal attachments. It is possible that sudden tensing of the mitral leaflets or annulus produced the sound (Figure 7B). Although this mechanism is feasible, the timing of the sound with respect to the prolapse of the

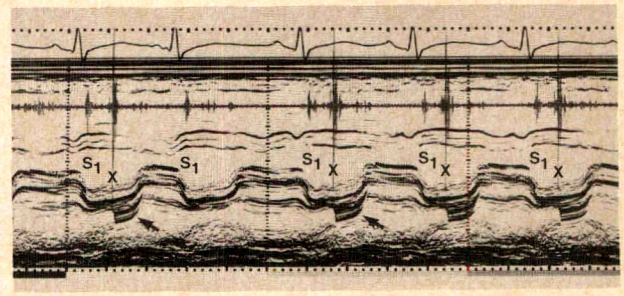
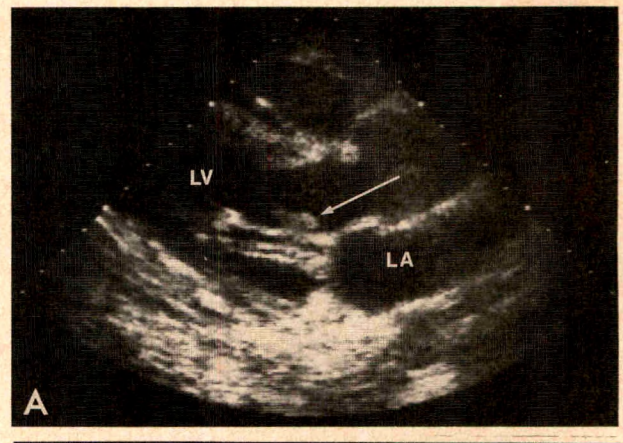


FIGURE 2. Simultaneous echo-phonocardiogram from apex in case 1. Mitral stenosis is present. High-frequency, high-amplitude systolic sound (X) is seen on beats 1, 3, 4 and 5 in association with mass *(arrow)* prolapsing into left atrium. Systolic sound begins as mass "disengages" from mitral valve. S_1–X interval varies from 110 to 130 ms coincident with variable timing of mass prolapse during systole. During premature atrial contraction (beat 2), mass does not prolapse, and loud systolic sound is clearly absent.



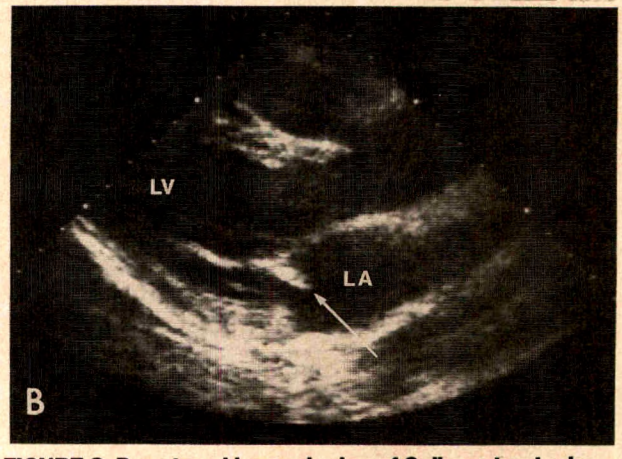


FIGURE 3. Parasternal long-axis view of 2-dimensional echocardiogram during end-diastole *(A)* and systole *(B)* in case 2. Mass *(arrow)* attached to anterior leaflet of mitral valve prolapses into left atrium (LA) during systole. LV = left ventricle.

mass appears inconsistent, because the sound should occur at the time of maximum "tugging" (during the maximum posterior displacement of the mass into the left atrium). However, both the onset of the sound and the time of its peak amplitude occurred before maximum prolapse of the mass (Figures 2 and 6).

The atypical clicks could be a result of delayed closure of 1 leaflet of the mitral valve (Figure 7C). Delayed mitral valve closure that occurs in mitral stenosis produces a loud first heart sound.[7] This is thought to be a result of increased leaflet velocity associated with the increased rate of left ventricular pressure increase (dP/dt), or the higher pressure gradient between the left ventricle and atrium at the time of delayed mitral valve closure.[13] If the mass interfered with normal mitral valve closure, then closure later in systole could produce a loud sound because of the large pressure gradient between the left ventricle and atrium at this time. This sound would occur at the time of disengagement of the mass from the mitral valve, because this is when delayed closure would occur. Although this mechanism is consistent with the timing of the sound production, it is unlikely for several reasons. First, the amplitude of S_1 should be decreased on beats when the mass prolapsed (and closure of 1 leaflet occurred later in systole), because the normal contribution of this mitral leaflet to S_1 would be absent. Varying intensity of S_1 was not noted in any of the cases. Second, in patient 1, the mass did not engage the mitral valve until after the valve had already closed (Figure 1B), and hence, the mass did not interfere with normal closure of a mitral leaflet.

To determine the mechanism of sound production, one must look for the mechanical event that coincided with the onset (not the peak amplitude) of the sound. In all cases, the onset of the sound coincided with disengagement of the mass from the mitral valve. Figure 7D shows how a mitral valve mass could produce the sound. As the mass engaged the mitral valve, it either prolapsed through a preexisting orifice or moved 1 of the mitral leaflets to create an orifice. We propose that the mass opened the mitral valve in a "reverse" direction by forcing a mitral leaflet toward the left atrium. This would generate great leaflet tension and a forceful recoil (a loud sound) as the leaflet returned to its normal position (toward the left ventricle) during disengagement and prolapse of the mass. The mechanism of sound production would be similar to the sound produced by a baseball card and the spoke of a bicycle wheel. As the wheel turns, the spoke (mass) moves the card (mitral leaflet) in the direction of the turning spoke. After the spoke moves past the card (disengages from valve), the abrupt release of tension produces a loud sound during the return of the card

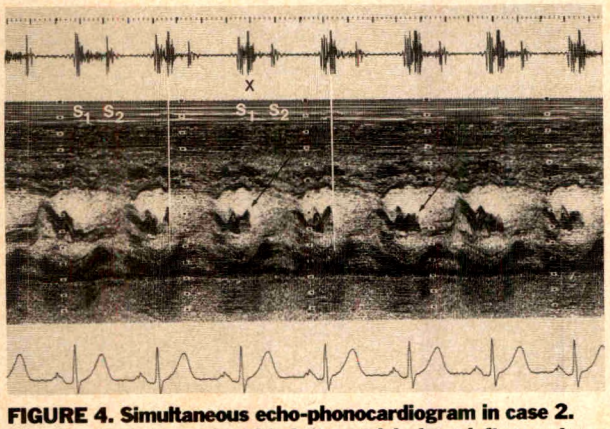


FIGURE 4. Simultaneous echo-phonocardiogram in case 2. Mitral valve is imaged within left ventricle from left parasternal window. Systolic sound (X) is present on all beats, except first. Associated with this sound is mass *(arrow)* present in left ventricle in plane of mitral valve. Onset of extrasystolic sound corresponds with mass leaving left ventricle and "disengaging" from mitral valve. S_1–X interval varies coincident with variable timing of prolapse of mass. On first beat, extrasystolic sound is absent, and this beat does not show mass engaged with mitral valve.

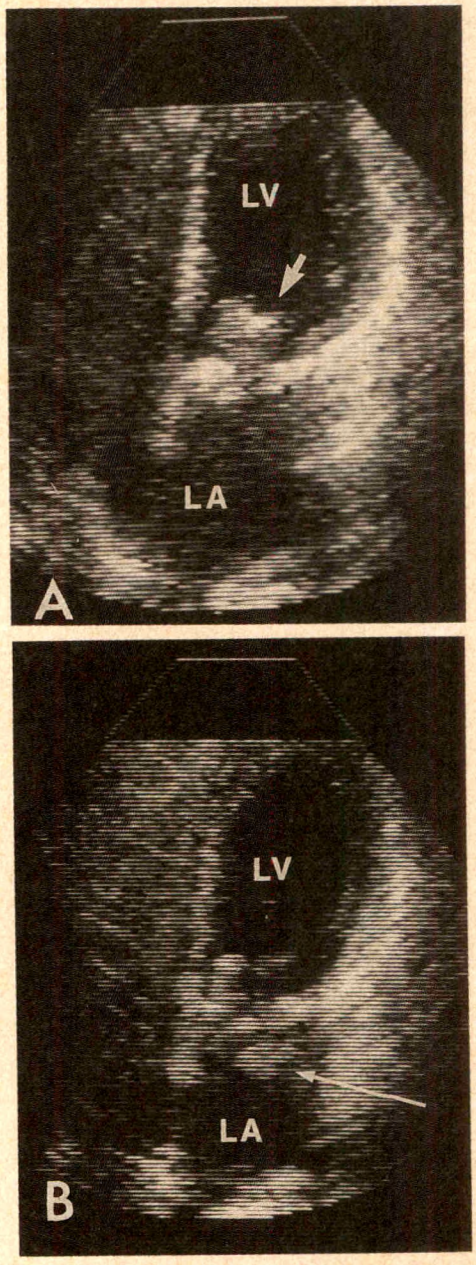


FIGURE 5. Apical 4-chamber echocardiogram during end-diastole *(A)* and systole *(B)* in case 3. Mass *(arrow)* associated with bioprosthetic mitral valve prolapses from left ventricle (LV) into left atrium (LA) during systole.

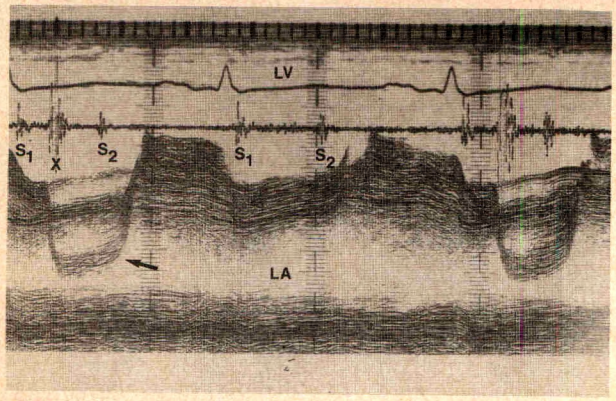


FIGURE 6. Echo-phonocardiogram from apical window in case 3. Mass *(arrow)* moves from left ventricle (LV) to "engage" mitral valve in early systole and then prolapses into left atrium (LA) during mid-systole. Extra heart sound (X) begins as mass "disengages" from mitral valve. Sound does not occur on beat 2, when mass engages valve, but does not prolapse.

(mitral leaflet) to its original position. This mechanism of sound production could explain why: (1) the sound begins immediately on disengagement of the mass from the mitral valve, and (2) the sound occurs only on beats when the mass prolapses, and not also on beats when the mass strikes the valve, but does not prolapse.

These cases suggest that an atypical or intermittent systolic click can be an important physical examination finding associated with prolapsing mitral valve masses. This entity should be considered together with mitral valve prolapse in the differential diagnosis of a systolic click.

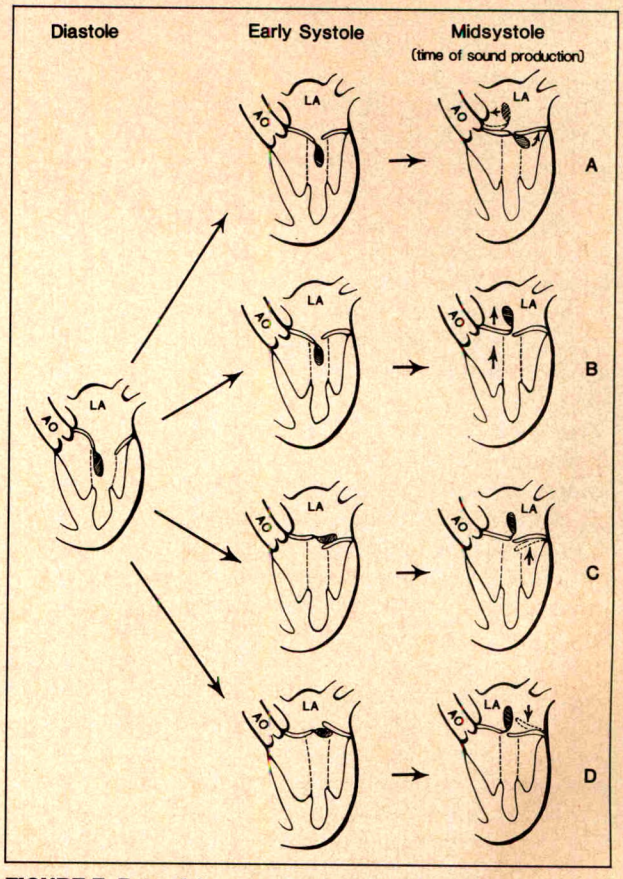


FIGURE 7. Potential mechanisms for systolic click. *Arrows in last column* point to structure and movement that produce sound with each proposed mechanism. *A,* sound is produced by mass striking either mitral valve or left atrium (LA). *B,* mass "tugs" on either chordae tendinae or attached mitral valve/annulus. *C,* mass interferes with normal mitral valve closure and delays closure until later in systole. *D,* sound is produced by tensing of mitral leaflet (posterior leaflet) during "engagement" of mass with valve in early systole and then abrupt movement of leaflet toward left ventricle as mass "disengages" from valve, and leaflet returns to normal position. AO = aorta.

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Transesophageal Versus Transthoracic Echocardiography for Diagnosing Mitral Valve Perforation

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Perforation of a mitral valve leaflet is uncommon. Most perforations are the result of bacterial endocarditis. Although mitral regurgitation is readily diagnosed by Doppler echocardiography, identification of leaflet perforation by conventional transthoracic echocardiography (TTE) may be difficult. Limitations in resolution, reverberatory echoes and signal dropout may contribute to this problem.[1] Improved visualization of mitral valve pathology by transesophageal echocardiography (TEE) has been well documented in patients with bacterial endocarditis.[2–4] In this study of 10 patients with mitral valve perforation we compared the diagnostic sensitivity of TTE with that of TEE for the demonstration of mitral valve perforation, valvular vegetation and mitral valve aneurysm. We also report an association of aortic regurgitation with mitral valve perforation.

TTE was performed using a 2.5 or 3.5 MHz transducer via the standard echocardiographic windows. TEE was performed with a 5.0 MHz monoplane transesophageal transducer. The 2-dimensional image of perforation was defined as an interruption of leaflet continuity at a site removed from the commissures (Figure 1A). The color flow Doppler image of a perforation was defined as a high-velocity turbulent jet traversing a valve leaflet in systole (Figure 1B). A vegetation was diagnosed when a localized mobile mass, usually with independent motion, appeared attached to a valve leaflet (Figure 2). Mitral valve aneurysm was defined as a discreet bulging of a leaflet maintained outside its normal contour in both systole and diastole[5] (Figure 3).

Ten consecutive patients with mitral valve perforation diagnosed by echocardiography are included in this study. They all were referred for evaluation of suspected infective endocarditis. Patient data are presented in Table I.

TTE was performed in all 10 patients; all but 1 study included color flow Doppler imaging. Perforation of the mitral valve was identified in 3 patients (30%) and was localized to the anterior leaflet in all 3. Mitral regurgitation was found in all patients studied by color flow Doppler imaging and was mild in 2, moderate in 6 and severe in 1. Greater than trace aortic regurgitation was found in 5 patients (56%) and was severe in all 5 cases. Vegetations were identified by TTE in 7 patients (70%). An aneurysm of the mitral valve was identified by TTE in only 1 patient (10%), and was localized to the anterior leaflet. A perforation site was located within this aneurysm.

TEE with color flow imaging diagnosed mitral valve perforation localized to the anterior leaflet in all 10 patients. TEE showed mitral regurgitation in all 10 patients and aortic regurgitation in 6. The diameters of the mitral valve perforations ranged from 1 to 15 mm. Vegetations were identified in 9 patients (90%). None of the vegetations seen by TTE were missed by TEE. Aneurysms of the mitral valve were found by TEE in 5 pa-

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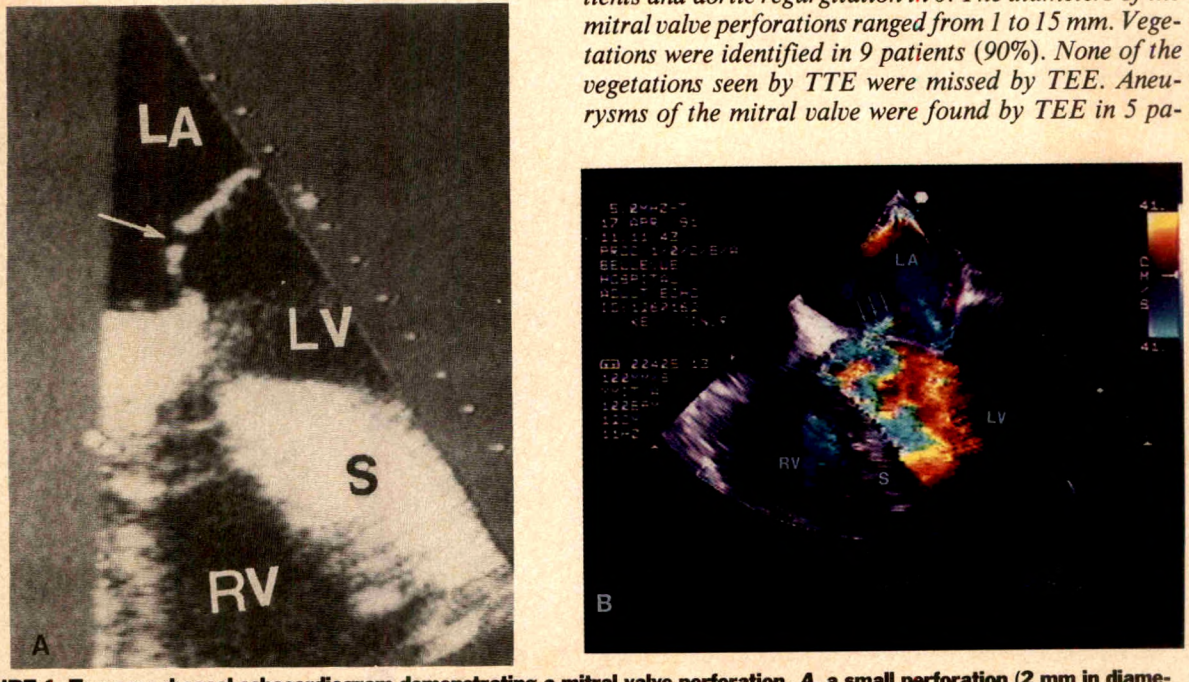


FIGURE 1. Transesophageal echocardiogram demonstrating a mitral valve perforation. *A*, a small perforation (2 mm in diameter) is noted in the anterior mitral leaflet *(arrow)*. B, a small perforation with color flow Doppler imaging added. A high-velocity jet traverses the perforation *(arrows)*. LA = left atrium; LV = left ventricle; RV = right ventricle; S = interventricular septum.

TABLE I Clinical Characteristics of Patients

Pt.	Age (yr) & Sex	History of Valve Disease	Perforation TTE	Perforation TEE	Defect Size (TEE) (mm)	Aneurysm TTE	Aneurysm TEE	AV Veg. TTE	AV Veg. TEE	MV Veg. TTE	MV Veg. TEE	Regurgitation by Color Imaging AV	Regurgitation by Color Imaging MV	Bacteriology	Follow-Up MVR	Follow-Up AVR	Follow-Up Died
1	46M	AVR for AR	0	+	3	0	0	0	0	+	+	0	Moderate	Strep. viridans	+	+	0
2	33M	Bicuspid AV	0	+	1	0	+	0	0	0	0	Severe	Mild	Staph. epidermidis*	0†	+	0
3	74F	0	0	+	2	0	+	+	+	0	0	Severe	Moderate	Strep. faecalis	+	+	+
4	53M	0	+	+	2	0	0	+	+	0	0	Severe	Moderate	Strep. viridans	+	+	0
5	47F	MVP	0	+	2	0	0	0	0	0	+	Trace	Moderate	0‡	0	0	0
6	30M	AVR for AR	0	+	2	0	0	0	0	+	+	0	Mild	Alpha strep. group D	0	0	0
7	50M	0	0	+	2	0	+	+	+	0	+	Moderate	Severe	Klebsiella sp.	0	0	+
8	48M	0	+	+	5	0	0	+	+	+	+	Severe	Moderate	Strep. bovis	+	+	0
9	43F	0	+	+	15	+	+	0	0	0	+	0	Severe	0‡	+	0	0
10	41M	0	0	+	2	0	+	0	+	+	+	Severe	Moderate	Staph. aureus	+	+	0

*Tissue culture.
†Mitral valve repair procedure.
‡Received prior antibiotics.
AR = aortic regurgitation; AV = aortic valve; AVR = AV replacement; MV = mitral valve; MVP = mitral valve prolapse; MVR = MV replacement; sp. = species; Staph. = staphylococcus; Strep. = streptococcus; TEE = transesophageal echocardiography; TTE = transthoracic echocardiography; Veg. = vegetation; + = present; 0 = absent.

tients (50%), including the one diagnosed by TTE. They all involved the anterior leaflet and measured from 4 to 20 mm in diameter. The perforation site was located within the aneurysm in all 5 patients.

Thus, TEE demonstrated a greater diagnostic yield than TTE. Mitral valve perforations were found in all 10 patients by TEE but in only 3 by TTE (100 vs 30%). Mitral valve vegetations were diagnosed by TEE in 7 patients but in only 4 by TTE (70 vs 40%). Aneurysms were identified in 5 patients by TEE but in only 1 by TTE (50 vs 10%). In addition, aortic valve vegetations were demonstrated by TEE in 5 patients and by TTE in 4 (50 vs 40%).

Seven patients underwent valve surgery and 3 received medical therapy after mitral valve perforation was diagnosed. Pathologic studies were obtained in all 7 patients who underwent cardiac surgery. In all of these cases the mitral valve perforations as well as the presence or absence of vegetations were confirmed. Of the 5 patients with mitral valve aneurysms diagnosed by TEE, 4 underwent cardiac surgery. In 3 patients the aneurysms were confirmed and in the fourth (no. 10) the mitral valve was removed piecemeal and could not be evaluated for aneurysm formation at pathologic examination. A single patient (no. 4) had a "small aneurysm" diagnosed at the time of surgery that had not been diagnosed by either echocardiographic approach.

Mitral valve perforation is not often clinically diagnosed before open heart surgery or postmortem examination. However, autopsy studies of patients who have died of endocarditis document a prevalence of mitral valve perforation from 8 to 20%,[6] suggesting that this complication may not be rare. Two-dimensional TTE has long been the mainstay of the noninvasive evaluation of the mitral valve. However, its sensitivity for the diagnosis of mitral valve perforation is low and limited by poor image resolution.[1] More recently, the use of color flow Doppler imaging has increased the sensitivity of TTE for the diagnosis of mitral valve perforation. A high-velocity systolic jet traversing a valve leaflet indicates perforation even if the anatomic defect cannot be clearly seen by 2-dimensional imaging.[1,7] Jain et al[1] diagnosed mitral valve perforations in 3 patients using color flow imaging with 2-dimensional TTE.[1] The sizes of the defects were all confirmed at pathologic study and ranged from 3 to 7 mm. In our group of patients, the 3 perforations that could be shown by TTE ranged from 2 to 15 mm in diameter.

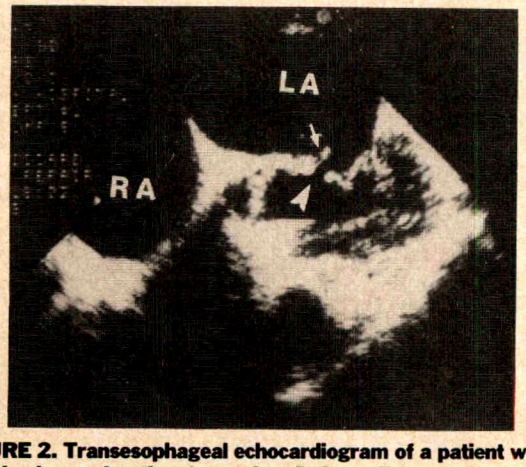


FIGURE 2. Transesophageal echocardiogram of a patient with mitral valve perforation *(arrowhead)*. A small vegetation is noted on the atrial side of the perforation *(small arrow)*. LA = left atrium; RA = right atrium.

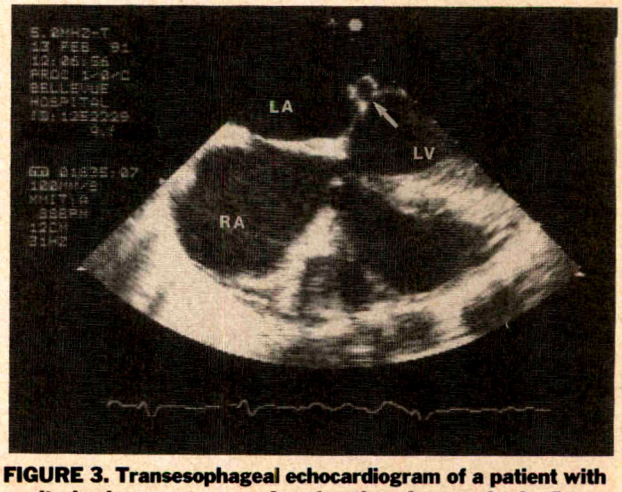


FIGURE 3. Transesophageal echocardiogram of a patient with a mitral valve aneurysm and perforation. An anterior leaflet aneurysm *(arrow)* is clearly seen. LA = left atrium; LV = left ventricle; RA = right atrium.

However, those 7 additional perforations diagnosed by TEE alone ranged in size from 1 to 3 mm. Six of these 7 measured only 1 or 2 mm. This trend indicates that the finer resolution of TEE may translate directly into enhanced diagnostic capabilities. In fact, the correlation between the pathologic findings and the TEE findings in our study is excellent. All of the perforations and vegetations were confirmed in the 7 patients who underwent cardiac surgery.

Vegetations of bacterial endocarditis are usually attached to the free margin of a leaflet.[8] Destruction of the leaflet body should ensue as infection spreads from the leaflet edge. By contrast, the region of destruction appears within the body of the leaflet in all patients presented in this report. This suggests that the pathogenesis of mitral valve perforation may be somewhat different from that which pertains to other forms of valve destruction from infectious endocarditis.

Endocardial surfaces struck by jets of high-velocity turbulent blood flow are predisposed to bacterial infection.[9,10] Aortic regurgitation jets often hit the ventricular surface of the anterior mitral valve leaflet. With use of TEE, our laboratory has demonstrated a vegetation at the base of the anterior leaflet of the mitral valve, exactly where a jet of aortic regurgitation appeared to strike it.[11] Reid et al[5] suggested the same pathogenesis for mitral valve aneurysm with and without perforation.

Eight of the 10 patients (80%) presented in this study had significant aortic regurgitation either at the time of our study or beforehand, necessitating aortic valve replacement. Also, all of the perforations were located in the anterior mitral valve leaflet. This may lend support to the suggestion of a pathogenetic relation between aortic regurgitation and mitral valve perforation.

In conclusion, TEE has a higher diagnostic yield of mitral valve perforation when compared with TTE, and perforations as small as 1 mm in diameter can be seen. There is an association between aortic regurgitation and perforation of the anterior leaflet of the mitral valve, although a pathogenetic relation cannot be claimed. TEE is indicated when mitral valve perforation is suspected and TTE fails to demonstrate it. Moreover, TEE should be considered for the evaluation of the mitral valve in all patients with aortic regurgitation in the setting of endocarditis.

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Abnormal Blood Rheology in Idiopathic Dilated Cardiomyopathy

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Thromboembolic events represent a frequent complication in dilated cardiomyopathy.[1] Intracardiac thrombi occur in a high proportion of patients[2,3] and are primarily ascribed to a reduction in cardiac output with low intracardiac blood flow velocity.[4] Hemorrheologic factors are known to play an important role in the coagulation process, particularly in presence of low flow states.[5] Hemorrheologic abnormalities in patients with dilated cardiomyopathy may therefore favor the generation of intracardiac thrombi. Such abnormalities in patients with low cardiac output might even further compromise peripheral blood flow and thus reduce tissue oxygen supply. Therefore, rheologic parameters were studied in patients with idiopathic dilated cardiomyopathy and compared with a healthy control group.

The study group consisted of 60 consecutive patients with idiopathic dilated cardiomyopathy. Clinical, echocardiographic and hemodynamic data of the study group are listed in Table I. Diagnosis was based on the following echocardiographic criteria: diffuse dilatation and hypokinesia of the left ventricle, parasternal left ventricular end-diastolic diameter >56 mm, and left ventricular fractional shortening <26%. Patients with significant valvular heart disease (except for relative valvular incompetence), arterial hypertension, acute myocarditis and significant coronary artery disease (coronary luminal diameter reduction >50%) were excluded. Coronary angiography was performed in 46 patients, but was not routinely done in young patients without clinical suspicion. Furthermore, patients with arterial occlusive disease, patients taking hemorrheologically

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Manuscript received October 23, 1991; revised manuscript received and accepted February 10, 1992.

TABLE I Clinical, Echocardiographic and Hemodynamic Characteristics of 60 Patients with Idiopathic Dilated Cardiomyopathy

Age (years)	51 ± 12
Men/women (n)	51 (85%)/9 (15%)
New York Heart Association class	
I (no. of pts.)	6 (10%)
II (no. of pts.)	35 (58%)
III (no. of pts.)	16 (27%)
IV (no. of pts.)	3 (5%)
Anticoagulants (n)	23 (38%)
Atrial fibrillation (n)	25 (42%)
Intracardiac thrombus (n)	10 (17%)
Left ventricular end-diastolic diameter (mm)	69.0 ± 10.6
Fractional shortening (%)	13.1 ± 6.1
Left atrial diameter (mm)	48.4 ± 9.1
Cardiac index (echocardiography) (liters/min/m^2)	2.4 ± 0.8
Mean right atrial pressure (mm Hg)	7.9 ± 4.1
Mean pulmonary artery pressure (mm Hg)	29.1 ± 10.7
Mean pulmonary wedge pressure (mm Hg)	21.4 ± 8.3
Cardiac index (thermodilution) (liters/min/m^2)	2.7 ± 0.9

All values are mean ± standard deviation.

active drugs as well as smokers and patients with diabetes and hyperlipidemia were excluded. Patients receiving oral anticoagulation (n = 23) were not excluded because this medication has no effect on rheologic parameters.[6] However, almost all patients were treated with diuretic drugs and angiotensin-converting enzyme inhibitors.

An age- and sex-matched group of 25 healthy subjects (21 men and 4 women aged 50 ± 17 years) served as control subjects. They were all nonsmokers and there was no evidence of metabolic, neoplastic or inflammatory diseases.

All patients gave informed consent. Blood samples were obtained without stasis in the sitting position from a large cubital vein through a 19G cannula. Plasma fibrinogen was measured according to the method of Clauss.[7] Plasma viscosity was determined from diaminetetraacetic acid plasma with a Coulter-Harkness viscometer at 25°C.[8] Red cell aggregation was measured using the MA1-Aggregometer (Myrenne Roetgen, Federal Republic of Germany).[9] Measurements were obtained from heparinized blood (10 U/ml) with autologous plasma at stasis and at a low shear rate of 3/s. Whole blood viscoelasticity was determined from diaminetetraacetic acid blood at 25°C with an oscillating capillary viscometer (OCR-D, Paar, Graz, Austria) at a constant frequency of 2 Hz and shear rates of 2, 50 and 150 z/s.[10] All measurements were repeated after adjustment to a standard hematocrit of 45%.

Transthoracic echocardiography was performed on a Vingmed 800 system (Diasonics) using a 3.0 MHz transducer. Left ventricular end-diastolic and end-systolic diameters, left ventricular fractional shortening and left atrial diameter were obtained from parasternal M-mode recordings accoring to standard criteria.[11] Cardiac output was calculated by aortic valve area, velocity time integral of systolic aortic valve flow, and heart rate. Results are listed in Table I.

Right-sided cardiac catheterization was performed in 25 patients. Mean values for right atrial, mean pulmonary artery and pulmonary capillary wedge pressures and cardiac index are listed in Table I.

Results are expressed as mean ± SD. Comparison between groups was performed with the t test for unpaired data. Chi-square analysis was used for comparison of nonparametric variables. A p value <0.05 was considered significant.

Comparison of various hemorrheologic parameters between patients with idiopathic dilated cardiomyopathy and the control population is listed in Table II. Plasma fibrinogen, plasma viscosity, red cell aggregation and whole blood viscoelasticity at all shear rates were found to be significantly elevated in the patient group. These abnormalities persisted even after correction to a constant hematocrit of 45%.

TABLE II Comparison of Hemorheologic Variables in 60 Patients with Idiopathic Dilated Cardiomyopathy with Those in 25 Healthy Control Subjects

Variable	DCMP	Controls	p Value
Fibrinogen (g/liter)	3.66 ± 0.85	2.61 ± 0.48	p<0.001
Plasma viscosity (mPa s)	1.79 ± 0.14	1.66 ± 0.13	p<0.001
Hematocrit (%)	47.3 ± 5.04	45.7 ± 3.05	NS
RCA/stasis (a.u.)	6.28 ± 1.11	5.18 ± 1.11	p<0.001
RCA/low shear (a.u.)	8.77 ± 1.92	7.79 ± 1.63	p<0.05
RCA/stasis/hct45% (a.u.)	6.74 ± 1.22	5.52 ± 1.30	p<0.001
RCA/low shear/hct45% (a.u.)	9.95 ± 2.00	8.51 ± 2.01	p<0.01
WBVvils (mPa s)	13.2 ± 3.09	10.9 ± 1.45	p<0.001
WBVvims (mPa s)	7.89 ± 1.48	6.53 ± 0.66	p<0.001
WBVvihs (mPa s)	6.72 ± 1.16	5.63 ± 5.10	p<0.001
WBVells (mPa s)	5.31 ± 2.08	3.72 ± 0.69	p<0.001
WBVelms (mPa s)	3.19 ± 1.93	2.16 ± 0.64	p<0.01
WBVvils/hct45% (mPa s)	12.4 ± 2.10	10.7 ± 0.84	p<0.001
WBVvims/hct45% (mPa s)	7.46 ± 0.96	6.42 ± 0.38	p<0.001
WBVvihs/hct45% (mPa s)	6.43 ± 0.77	5.59 ± 0.31	p<0.001
WBVells/hct45% (mPa s)	4.63 ± 1.51	3.58 ± 0.50	p<0.001
WBVelms/hct45% (mPa s)	2.82 ± 1.71	2.05 ± 0.62	p<0.001

All values are mean ± standard deviation.
a.u. = arbitary units; DCMP = dilated cardiomyopathy; hct45% = measurement performed after correction to a hematocrit of 45%; mPa s = millipascal seconds; NS = not significant; RCA/low shear = red cell aggregation at low shear rate (2/s); RCA/stasis = red cell aggregation at stasis; WBVells = elastic component of whole blood viscosity at low shear rate (3/s); WBVelms = elastic component of whole blood viscosity at medium shear rate (50/s); WBVvihs = viscous component of whole blood viscosity at high shear rate (150/s); WBVvils = viscous component of whole blood viscosity at low shear rate (2/s); WBVvims = viscous component of whole blood viscosity at medium shear rate (50/s).

Within the group of patients having dilated cardiomyopathy, rheologic abnormalities showed no correlation with clinical (New York Heart Association class, duration of disease, history of embolism, heart rate and presence of atrial fibrillation), echocardiographic (left ventricular diameter, left atrial diameter, left ventricular ejection fraction and cardiac index) or hemodynamic parameters (right atrial, mean pulmonary artery and pulmonary capillary wedge pressures and cardiac index). No difference was observed in the degree of rheologic abnormalities between patients with (n = 10) and without (n = 50) intracardiac thrombi.

The present study indicates the existence of significant hemorrheologic abnormalities in patients with idiopathic dilated cardiomyopathy. Plasma fibrinogen concentration, plasma viscosity, whole blood viscoelasticity and red cell aggregation were found to be consistently higher when compared with values obtained from a sex- and age-matched healthy control group.

Plasma fibrinogen constitutes a major determinant of plasma viscosity, whole blood viscosity and red blood cell aggregation, and therefore hyperfibrinogenemia may be considered as an important underlying abnormality. Hyperfibrinogenemia was observed previously in patients with cardiac failure,[12,13] but its etiology still remains to be elucidated. Diuretic treatment may lead to a reduction in plasma volume and thus may cause elevated fibrinogen levels.[13] However, the rheologic abnormalities observed in the present study are unlikely to be simply caused by hemoconcentration, since hematocrit values were not found to be significantly higher in the patient group. Within the group of patients having dilated cardiomyopathy, there was no correlation between the degree of rheologic abnormalities and clinical, echocardiographic or hemodynamic parameters, respectively. Therefore, one might speculate that the observed rheologic abnormalities may not be due to the hemodynamic impairment seen in these patients, but that other factors (e.g., chronic inflammatory myocardial disease) may play an instrumental role.

The present results may have 2 potential clinical implications: First, echocardiographic and autopsy studies in dilated cardiomyopathy have shown a high incidence of intracardiac thrombi.[2,3] This was attributed to a decrease in ventricular wall motion amplitude and to the low blood flow velocity within the dilated cardiac chambers.[4] Rheologic abnormalities may be an additional factor in thrombus formation. However, no difference was observed in the degree of rheologic abnormalities between patients with and without intracardiac thrombi. Because rheologic factors are supposed to play only a modifying role for thrombus generation, a larger number of patients will be needed to clarify this issue.

Second, hemorrheologic factors substantially affect peripheral blood flow. In patients with dilated cardiomyopathy and low cardiac output, peripheral blood flow may already be critically reduced. Rheologic abnormalities may even further compromise organ perfusion and limit the oxygen supply of peripheral tissues. In respect to this, oxygen desaturation was demonstrated in working muscles of patients with heart failure.[14]

In conclusion, the present data demonstrate the existence of hemorrheologic abnormalities in patients with idiopathic dilated cardiomyopathy. More studies are required to clarify the underlying etiology and to evaluate the prognostic and therapeutic implications of this finding.

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Left Ventricular Shape in Idiopathic Dilated Cardiomyopathy and Cardiomyopathy With or Without Only Mild Ventricular Dilatation

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Left ventricular (LV) dilatation and diffuse LV hypokinesia have been considered characteristic features of "congestive" cardiomyopathy, as originally described by Goodwin et al.[1] Since the mid-1970s, the term congestive cardiomyopathy has been increasingly replaced by "dilated cardiomyopathy." Recently, Keren et al[2] called attention to an entity they designate "mildly dilated congestive cardiomyopathy," defined as end-stage heart failure of unknown etiology occurring with neither typical

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Manuscript received November 8, 1991; revised manuscript received January 27, 1992, and accepted January 28.

TABLE I Various M-Mode and Two-Dimensional Echocardiographic Measurements in the Three Groups of Patients

	Control Subjects		Congestive Nondilated Cardiomyopathy		Congestive Dilated Cardiomyopathy	
	Mean ± SD	p Value	Mean ± SD	p Value	Mean ± SD	p Value*
BSA (m^2)	1.87 ± 0.14	NS	1.87 ± 0.2	NS	1.46 ± 0.19	NS
LVID (cm)	4.93 ± 0.46	<0.02	5.25 ± 0.34	<0.000	6.57 ± 0.69	<0.000
LVID/m^2 (cm)	2.65 ± 0.28	NS	2.84 ± 0.33	<0.000	3.4 ± 0.49	<0.000
FS (%)	37.2 ± 6.2	<0.000	19.4 ± 4.9	NS	18.7 ± 5.6	<0.000
LV mass/m^2	1117 ± 19	<0.000	167 ± 34	<0.01	206 ± 58	<0.05
2-dimensional apical chamber						
L (cm)	7.96 ± 0.69	NS	7.97 ± 0.71	NS	8.42 ± 0.73	NS
D2 (cm)	4.4 ± 0.47	<0.000	5.14 ± 0.53	<0.005	5.74 ± 0.8	<0.000
LV area (cm^2)	31.4 ± 5.8	<0.01	36.5 ± 5.9	<0.001	42.9 ± 7.3	<0.000
D1 + D2 + D3 (cm)	12.59 ± 1.25	<0.000	14.7 ± 1.61	<0.000	16.64 ± 1.99	<0.000
D2/L†	0.55 ± 0.06	<0.000	0.65 ± 0.07	NS	0.69 ± 0.11	<0.000
LV area/L^2†	0.50 ± 0.05	<0.02	0.56 ± 0.1	NS	0.59 ± 0.14	<0.01
(D1 + D2 + D3)/3L	0.52 ± 0.05	<0.000	0.62 ± 0.08	NS	0.66 ± 0.09	<0.000
2-dimensional apical long axis						
L (cm)	8.07 ± 0.44	NS	8.4 ± 0.8	NS	8.62 ± 0.92	<0.03
D2 (cm)	4.37 ± 0.27	<0.000	5.17 ± 0.65	<0.01	5.8 ± 0.86	<0.000
LV area (cm^2)	31.7 ± 3.2	<0.000	39.1 ± 1.72	NS	41.8 ± 11.6	<0.001
D1 + D2 + D3	12.69 ± 0.73	<0.000	14.81 ± 1.72	<0.005	16.7 ± 2.34	<0.000
D2/L†	0.54 ± 0.04	<0.001	0.62 ± 0.08	<0.05	0.68 ± 0.01	<0.000
LV area/L^2†	0.50 ± 0.05	<0.001	0.56 ± 0.07	NS	0.59 ± 0.08	<0.000
(D1 + D2 + D3)/3L†	0.53 ± 0.04	<0.001	0.56 ± 0.07	<0.02	0.65 ± 0.1	<0.000

*Comparison of dilated cardiomyopathy and normal groups.
†LV shape descriptors.
p values compare the nondilated cardiomyopathic group with normal and dilated cardiomyopathy groups.
BSA = body surface area; D1, D2 and D3 = transverse LV dimensions (see Figure 1); FS = fractional systolic shortening of LVID; L = LV length; LV = left ventricular; LVID = left ventricular internal dimension; NS = not significant.

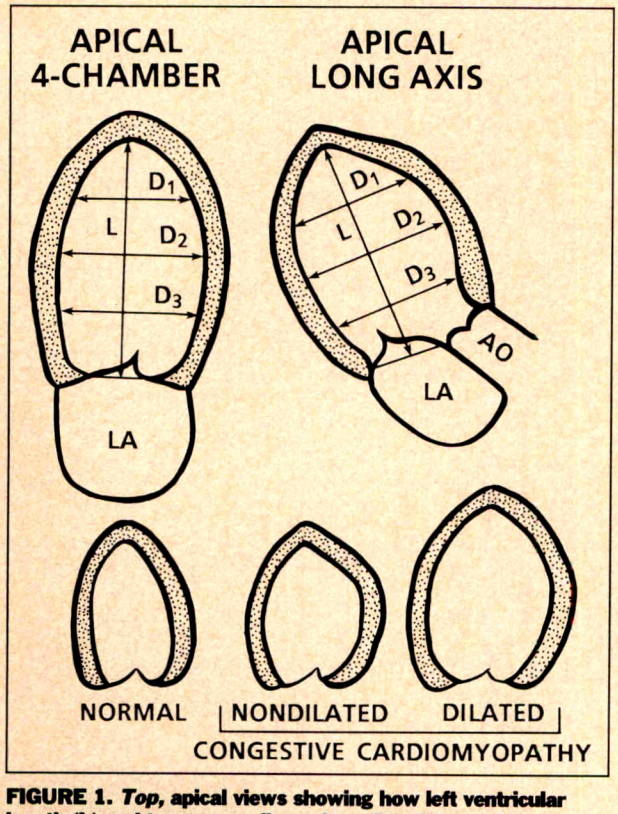


FIGURE 1. ***Top,*** **apical views showing how left ventricular length (L) and transverse dimensions (D1, D2 and D3) were measured; latter 3 lines divided left ventricular length in 4 equal parts.** ***Bottom,*** **left ventricular shape in normal man** ***(left),*** **patient with nondilated congestive cardiomyopathy** ***(center),*** **and patient with dilated congestive cardiomyopathy** ***(right).*** **Left ventricle is wider (more spherical) in latter 2 cases. AO = aortic root; LA = left atrium.**

hemodynamic findings of restrictive cardiomyopathy nor significant LV dilatation. They stated, "some of the patients in this series actually had cardiac dimensions within normal limits." We undertook the present echocardiography study to: (1) ascertain whether mildly dilated or nondilated congestive cardiomyopathy does in fact exist in our population, and (2) compare LV shape in such patients with those in patients with typical dilated cardiomyopathy and in normal subjects.

Our series consisted of 54 male veterans with: (1) symptoms and signs of chronic LV failure, (2) diffusely hypokinetic LV chambers, and (3) LV internal dimension systolic shortening fraction <26%. LV mass was estimated by the M-mode method described by Devereaux et al.[3] LV internal dimension was obtained from short-axis parasternal guided M-mode recordings at chordae tendineae LV level. In apical 4-chamber, as well as long-axis, views, the following measurements were performed using electronic calipers and planimetry: LV area and length (L), and 3 transverse LV dimensions (D1, D2 and D3) that divide L in 4 equal parts (Figure 1). The following ratios were used as LV shape descriptors: D2/L; (D1 + D2 + D3)/3L; and LV area/L^2. Cardiomyopathy patients were divided in 2 groups as follows: (1) LV internal dimension ≤56 mm on M-mode echocardiography (n = 25; nondilated cardiomyopathy), and (2) LV internal dimension >56 mm (n = 29; dilated cardiomyopathy). Eighteen men of comparable age with no evidence of heart disease on examination, electrocardiography and echocardiography constituted a control group. We excluded patients with the following: (1) regional LV wall motion abnormalities or obvious regional disparities in degree of hypokinesia, (2) evi-

dence of past myocardial infarction on electrocardiogram or enzyme estimations, and (3) LV wall or septal thickness >13 mm (i.e., all had normal or at most only mildly increased LV wall thickness). Coronary angiography was available in only 6 cardiomyopathic patients; normal coronary arteries were demonstrated in all 6.

Almost all cardiomyopathy patients were receiving digoxin and furosemide. Approximately two thirds of patients were also receiving captopril, lisinopril or vasodilators (nitrates or hydralazine), or a combination. No patient was receiving β blockers. Cardiomyopathy patients with LV internal dimension ≤56 mm were studied in our echocardiocardiography laboratory over a 3-year period. The other cardiomyopathy patients with LV internal dimension >56 mm were studied over a 10-month period.

There was no significant difference between the control and nondilated cardiomyopathy groups with respect to LV length. LV length was slightly greater in the dilated than in the nondilated cardiomyopathy group (p = not significant). By contrast, LV width (reflected in the transverse LV dimension D2 and in LV area) was significantly greater in nondilated cardiomyopathy patients than in control subjects, and even greater in dilated cardiomyopathy patients (consistent with an LV shape change from ellipsoidal toward spherical) (Table I).

Our LV shape descriptors revealed a significant difference in LV shape toward the spherical in the nondilated cardiomyopathy patients compared with that in the control group in both apical views. LV shape was slightly more spherical in dilated than in nondilated cardiomyopathy patients; however, this difference was not statistically significant in the apical 4-chamber view, and only significant in 2 of the 3 LV shape descriptors in the apical long-axis view ($p < 0.05$ and < 0.02, respectively). This suggests that the LV inflow plane (apical 4-chamber view) manifests less shape change toward the spherical than does the LV outflow plane (apical long-axis view). LV systolic performance (as reflected in the LV dimension systolic shortening fraction) was almost identical in the nondilated and dilated cardiomyopathy groups. This study reveals that a surprisingly large proportion of patients with the clinical and echocardiographic picture of dilated cardiomyopathy do not, in fact, have LV dilatation, if 5.6 cm is accepted as the upper limit of LV internal dimension by conventional parasternal M-mode recording. We are aware of the possibility that a patient's original (before onset of heart disease) baseline LV internal dimension of substantially <5.6 cm may dilate to ≤5.6 cm (e.g., 5 to 5.5 cm) during the cardiomyopathic process and be classified as nondilated cardiomyopathy, because the LV internal dimension is not >5.6 cm. That this actually happens is suggested by the fact that the mean values for LV area, width (D2) and sum of transverse dimensions (D1 + D2 + D3) are higher in the nondilated cardiomyopathy than in the control group. However, patients with a baseline LV internal dimension of 5.5 or 5.6 cm would be in the dilated cardiomyopathy category (>5.6 cm) after only slight LV dilatation. Nondilated cardiomyopathy patients had more hypertrophied LV chambers than did control subjects (mean LV mass 167 vs 117 g/m^2). It is possible that many or most of these nondilated cardiomyopathy patients had preexisting concentric LV hypertrophy before onset of the cardiomyopathic process, in which case, LV hypertrophy somehow limited or retarded LV dilatation. Alteration in LV shape toward the spherical has been demonstrated in dilated cardiomyopathy on the basis of simple LV length/width measurements obtained from angiocardiographic[4] or echocardiographic[5,6] images. Using LV shape descriptors similar to those used in this study, we showed significant differences between LV shape in normal and normally functioning dilated LV chambers, and in dilated cardiomyopathic LV chambers.[7] Our study confirms the findings of Keren et al[2] who found that there is a subgroup of patients with congestive cardiomyopathy with mild or no LV dilatation, and this may occur frequently. Furthermore, our study suggests that LV shape change toward the spherical occurs in such patients with LV internal dimension at the upper normal limit or less. Quantitative assessment of LV shape (using shape descriptors such as those in this study) could perhaps be of value in the echocardiographic diagnosis of this entity.

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Usefulness of the Electrocardiogram and Echocardiogram in Predicting the Amount of Interstitial Myocardial Collagen in Endomyocardial Biopsy Specimens of Patients with Chronic Heart Failure

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Myocardial fibrosis constitutes a nonspecific common pathway of myocardial response to injury. There is increasing evidence for the unfavorable effect of myocardial fibrosis on the outcome of patients with myocardial disease.[1] Adverse functional effects of myocardial collagen have been shown in systemic hypertension,[2] aortic valve stenosis,[3] idiopathic dilated cardiomyopathy[4] and other myocardial diseases.[5] However, initial and serial assessment of the severity of myocardial fibrosis is difficult in the absence of a practical and noninvasive method. Endomyocardial biopsy allows direct visualization and quantitation of the structural components of the myocardium. Using data obtained from endomyocardial biopsies in 24 patients, we sought to develop a noninvasive method of estimation of the degree of myocardial fibrosis.

Clinical data were obtained from the hospital records of the patients, all of whom were initially admitted to the cardiac surveillance unit for heart failure. All studies were performed during the same hospital admission.

The 24 patients (14 women [58%] and 10 men [42%]) were aged 19 to 77 years (mean 47). Duration of symptoms of heart failure ranged from 26 to 169 days (mean 119). Total 12-lead QRS voltage was measured by the method described by Siegel and Roberts.[6] Amplitudes of the QRS were standardized to 10 mm equaling 1 mV. Echocardiographicraphic measurements were performed according to the standard recommendations.[7,8] Endomyocardial biopsies were performed using a 9Fr Stanford bioptome. A mean of 4 ± 1 samples of right ventricular endomyocardium were obtained. Interstitial and total (endocardial + interstitial + perivascular) collagen volume fractions were quantified using Picro Sirius red-stained sections and a semiautomated computerized image analysis system.

For each variable, mean and SEM are reported. Correlations were calculated between QRS voltage, left ventricular mass and interstitial collagen volume fraction. A linear regression analysis of these 3 variables was performed. Student t *tests were used to evaluate differences in collagen volume fraction between different subgroups.*

In 15 patients with dilated cardiomyopathy, there was 4-chamber cardiac dilatation, reduced global ejection fraction with or without regional wall motion abnormalities, and normal epicardial coronary arteries. Four patients had lymphocytic myocarditis on biopsy. The remaining 5 patients had systemic hypertension and heart failure, despite normal left ventricular systolic function. No patient had ischemic, valvular or infiltrative heart disease.

Total collagen volume fraction ranged from 8 to 37% (mean 17). Patients with hypertensive heart disease had a significantly lower total collagen volume fraction than did those with dilated cardiomyopathy or myocarditis (12, 17.5 and 19%, respectively; $p = 0.0316$). Interstitial collagen volume fraction ranged from 5 to 27% (mean 12). Table I summarizes the electrocardiographic findings. There was no significant difference between interstitial collagen volume fraction in patients with or without conduction abnormalities ($n = 12$), pathologic Q waves ($n = 6$) or chamber hypertrophy ($n = 9$).

Table II summarizes the echocardiographic measurements, as well as the calculated left ventricular mass. Left ventricular mass ranged from 182 to 421 g. When the mass corresponding to collagen was subtracted from the total mass, the true left ventricular mass was obtained (range 159 to 394 g). Finally, the true left ventricular mass was corrected for the subject's height in meters. This corrected true left ventricular mass correlated significantly with 12-lead and precordial QRS voltage, but not with limb-lead voltage ($r = 0.75$, 0.64 and 0.42, respectively). Simple regression analysis showed an estimated equation of $Y = 0.7\times + 70$ between corrected true left ventricular mass and total QRS voltage ($r = 0.75$; $p < 0.0001$). The scatterplot for this rela-

TABLE I Electrocardiographic Findings in 24 Patients with Heart Failure

	Range (mean ± SEM)	No. (%)
Rhythm		
Sinus		21 (88)
Atrial fibrillation		2 (8)
Junctional		1 (4)
Left atrial enlargement		5 (21)
Right atrial enlargement		2 (8)
Left ventricular hypertrophy		9 (38)
PR interval > 21 ms		2 (8)
Left anterior fascicular block		1 (4)
Left posterior fascicular block		2 (8)
Left bundle branch block		4 (17)
Right bundle branch block		1 (4)
Nonspecific interventricular conduction delay		2 (8)
QRS axis	−35 to +140	
PR (ms)	10–24 (17 ± 1)	
QRS (ms)	6–16 (10 ± 1)	
QT (ms)	27–41 (35 ± 1)	
QTc (ms)	37–49 (44 ± 1)	
QRS voltage (mm)		
12-lead	63–183 (128 ± 8)	
V_1–V_6	39–143 (86 ± 6)	
Limb leads	11–81 (42 ± 4)	

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TABLE II Echocardiographic Measurements in 24 Patients with Heart Failure

	Range (mean ± SEM)
Left atrial diameter (mm)	30–59 (44 ± 2)
Left ventricular diastolic dimension (mm)	42–82 (64 ± 2)
Left ventricular systolic dimension (mm)	33–65 (51 ± 2)
Ventricular septal thickness (mm)	6–12 (9 ± 0.4)
Posterior wall thickness (mm)	7–12 (10 ± 0.3)
Left ventricular fractional shortening (%)	6–48 (21 ± 2)
Left ventricular mass (g)	182–421 (302 ± 14)
True left ventricular mass (g)	159–394 (270 ± 13)
True left ventricular mass/height (g/m)	98–219 (156 ± 7)

tion is shown in Figure 1. The 99% confidence interval for K = true left ventricular mass/(QRS voltage × height) was 1.28, 1.32. Based on this relation, the collagen volume fraction could then be estimated according to the equation: 1 − [1.3 (QRS voltage in mm × height in m)/left ventricular mass in g].

Pathologic remodeling of the cellular and extracellular matrix of the heart is a frequent histologic feature of myocardial diseases of different etiologies. The severity of these histologic changes may correlate with the clinical severity of the underlying cardiac disease,[1] as well as with other determinants of prognosis, such as hemodynamic data.[9] Myocardial fibrosis with or without myocellular hypertrophy indicates an adverse prognosis in patients with primary myocardial disease.[10] Increased volume fraction of collagen may indicate a reduced percentage of functioning myocytes and as such, determine the severity of the underlying damage to the myocardium.[9] Although determination of the ventricular systolic function can provide prognostic information in patients with myocardial disease, the course and outcome of the disease may not be adequately assessed in the individual patient.[1] Patients with preserved myocellular volume fraction may, in fact, improve over time, whereas significant decrease in the percentage of functioning myocardial cells is associated with a progressive course and an undesirable overall outcome.[1] Because the voltage generated on the electrocardiogram depends on the total mass of functioning myocardial cells, this relation may be used to estimate the severity of myocardial fibrosis when left ventricular mass is known. The correlation of the 12-lead QRS voltage to cardiac mass in patients with idiopathic dilated cardiomyopathy has been shown previously.[11] Thus, the noninvasive method described here may prove helpful in prognostication and follow-up of patients with various myocardial diseases.

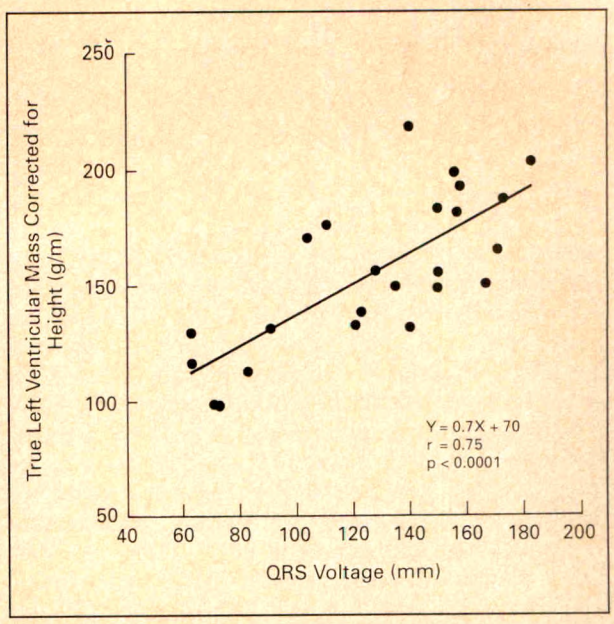


FIGURE 1. Scatterplot showing relation between true left ventricular mass corrected for height and 12-lead QRS voltage in 24 patients with heart failure.

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Intravascular Ultrasound Imaging of Guenther Vena Caval Filters

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The percutaneous implantation of vena caval filters has gained acceptance as a means of preventing pulmonary embolism in patients with contraindications to or inefficiency of oral anticoagulants. In the past years, we predominantly used the Guenther filter. Its stainless steel wires are formed into a helical basket and anchoring struts.[1] Our experience with 62 patients showed that this device prevents pulmonary embolism effectively. However, cranial and caudal migration of the filter, perforation of the caval wall by the struts, and breakage of the struts have been reported. In 39% of cases, thromboemboli were found inside the filter by computed tomography, but computed tomographic imaging does not allow differentiation between trapped emboli and genuine thrombi.[2]

Intravascular ultrasound has demonstrated reliable implementation in the diagnosis of peripheral arterial diseases.[3,4] McCowan et al[5] examined 6 different vena caval filters in vitro and in vivo, and found this method to be superior to both external ultrasound and cavography in detecting thrombi in the filter or vena cava. The present study was performed to assess the implementation of intravascular ultrasound imaging of Guenther basket filters, while paying particular attention to both the detection of trapped or genuine thromboemboli, and the diagnosis of filter perforation and breakage of struts.

Intravascular ultrasound was performed using an 8Fr fixed guidewire catheter system (Cardiovascular Imaging System, Inc., Sunnyvale, California) with a 20 MHz 2-dimensional rotating mirror intravascular ultrasound probe. Nine consecutive patients (7 men and 2 women, average age 75.2 ± 10.5 years, range 56 to 86) were studied with intravascular ultrasound. Images from the filter, and proximal and distal parts of the inferior vena cava were recorded and analyzed by 2 independent observers. Intravascular ultrasound results were compared with conventional radiographic and external Duplex ultrasound studies. Four subjects with suspected recurrent deep vein thrombosis underwent venography. Intravascular and Duplex ultrasound examinations, and venography were performed on the same day in all patients. After obtaining informed consent, the probing catheter was inserted through the jugular vein in 6 patients and by the femoral approach in 3. All filters could be reached with the probing catheter without difficulty, and the structures were clearly imaged by intravascular ultrasound. The main characteristics of the study group and the individual results are depicted in Table I.

Intravascular ultrasound showed the filter and the vena cava to be free from thrombotic structures in only 2 patients. In the other 7 subjects, thrombus formation of varying extent was found and could be classified into 3 types: (1) thromboemboli adherent to the wires or within the basket of the filter (n = 3). According to size and location in the caudal part of the basket, 1 thrombotic structure was interpreted as a trapped embolus. Small thrombi with a diameter of 2 to 5 mm were detected on the struts of another filter. The third patient had a floating thrombus originating from the steel wires of the filter (Figure 1). (2) Partial thrombosis of the vena cava by thrombus formation adjacent to the caval wall (n = 2), causing cross-sectional narrowing of 10 and 30%, respectively (Figure 2). Neither thromboembolic structure was detected by external Duplex ultrasound. (3) Total thrombotic occlusion of the vena cava distal to the filter (n = 2). Both caval filters were filled with thrombotic masses. In these cases, the filter could not be passed, but the probing catheter could be introduced in the proximal part of the thrombi, and the diagnosis of occlusion of the distal vena cava was accurately ascertained. The results were confirmed by cavography and by external Duplex ultrasound.

Filter breakage was visualized by intravascular ultrasound in 1 patient only, whereas plain abdominal radiography revealed 1 to 3 broken struts in 4 patients. Perforation of the caval wall to a depth of 6 mm by a

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TABLE I Main Characteristics of the Study Group and Intravascular Ultrasound Findings Compared with Plain Radiography and External Duplex Ultrasound

Pt.	Age (yr) Sex	Filter in Place (mos)	Heparin (H) Warfarin (W)	Plain Abdominal Radiography	External Duplex Ultrasound	Intravascular Ultrasound
1	86M	29	+ (H 5 days)	Tilted filter	Normal flow	Partial thrombosis at caval wall
2	75M	42	+ (W 7 mos)	1 broken strut	Normal flow	Small thrombus at strut
3	72M	9	+ (H 10 days)	Normal	Normal flow	Normal
4	62M	7	—	Normal*	No flow at filter level	Complete thrombotic occlusion at filter level
5	85F	43	+ (W 90 days)	2 broken struts	Normal flow	Thrombus in filter basket
6	73M	48	+ (W)	3 broken struts	Normal flow	1 broken strut
7	81M	17	+ (H 21 days)	Normal	Normal flow	Partial thrombosis at caval wall, perforation of strut
8	87M	37	+ (W 60 days)	1 broken strut	Normal flow	Partial thrombosis at caval wall
9	56F	48	+ (W)	Normal	No flow at filter level	Complete thrombotic occlusion at filter level

*Cavography revealed complete occlusion of the vena cava at filter level.

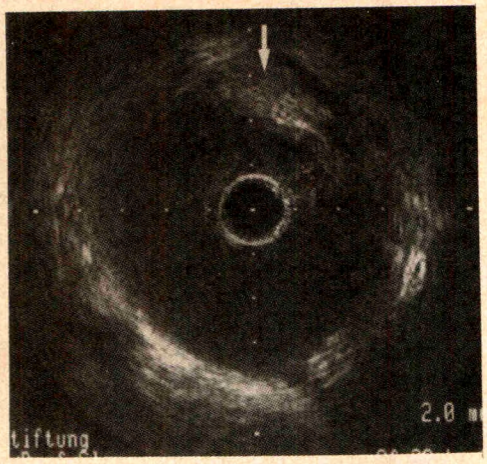


FIGURE 1. Intravascular ultrasound image recorded at site of Guenther vena caval filter. Partial thrombosis of vena cava by thrombus formation adjacent to caval wall *(arrow)*.

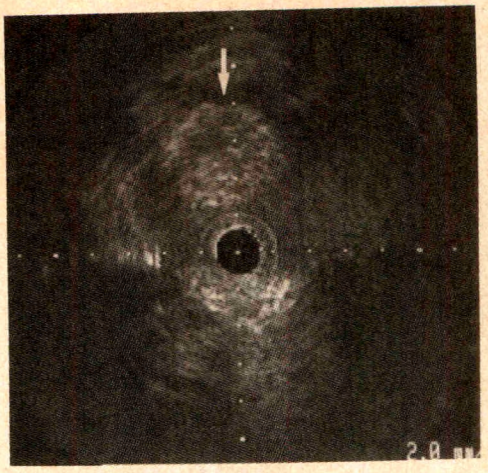


FIGURE 2. Intravascular ultrasound image of thrombus originating from steel wires of Guenther filter *(arrow)*.

strut was clearly diagnosed by intravascular ultrasound (Figure 3). This perforating strut was detected by neither conventional radiography nor external Duplex ultrasound. Intravascular ultrasound showed asymmetrically placed wires in 1 filter, which according to plain radiography was due to kinking of the filter.

The increasing number of implantations of vena caval filters needs accurate methods to evaluate long-term effectiveness and safety. Plain abdominal radiography can demonstrate migration and breakage of the filter, but provides no information on perforation and thrombus formation. External Duplex ultrasound is of limited value. Vorwerk et al,[6] using color-coded Duplex sonography in 15 patients, identified blood flow in the vena cava in 14 patients. A nearly total occlusion of the filter was demonstrated in 1 case, but partial thrombosis in another patient was missed. In our experience, intravascular ultrasound imaging may be implemented in patients with vena caval filters with the possibility of differentiating clearly the caval wall, filter structures and thrombus formation within and around the filter. The fixed guidewire intravascular ultrasound probing catheter passed the filter without any problem, and damage or dislocation of the filter, or break off of emboli did not occur. In our series, even small thrombi adherent to the steel wires of the basket and to the struts were visualized. It appears possible to differentiate between trapped emboli and genuine thrombi. Trapped emboli are found in the center or distal part of the basket, whereas genuine thrombi are more likely to adhere to the struts and caval wall. However, this assumption cannot be supported by our small study group. One perforation of the caval wall by a strut was missed by plain radiography and Duplex ultrasound, but was detected by intravascular ultrasound. Plain radiography revealed broken struts in 4 patients, and 3 of them were missed by intravascular ultrasound.

Intravascular ultrasound is a potentially valuable method in the detection of thrombus formation in vena caval filters and the vena cava itself. The method appears

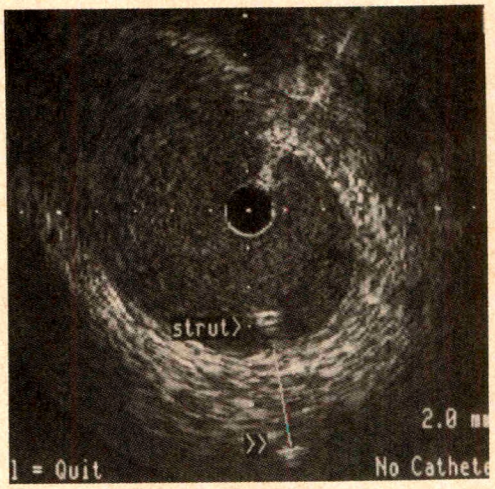


FIGURE 3. Intravascular ultrasound image of perforation of caval wall by strut *(>>)*. Another strut *(>)* is correctly located at cava wall.

to enable the diagnosis of perforation of the caval wall by the struts of the filter, but is less accurate in the assessment of filter breakage. A more extensive study is necessary to evaluate the possibility of differentiating trapped emboli from genuine thrombi by intravascular ultrasound.

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Maternal Left Ventricular Performance During Bicycle Exercise

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Over the last few years, more women are exercising during pregnancy. Although many studies have examined left ventricular (LV) function during exercise in nonpregnant subjects, to date there is minimal data available on the LV response in the pregnant patient exercising at a high level of intensity during the second half of pregnancy. Pregnancy has been compared to a state of volume overload resulting in an increase in LV size without significant hypertrophy of the LV walls.[1] This increase in radius-to-wall thickness ratio may be viewed as detrimental to LV emptying, because wall stress is directly proportional to this ratio.[2] To offset this change in LV shape, vascular resistance and mean arterial blood pressure are significantly reduced during pregnancy.[2] We hypothesized that strenuous exercise during the second half of pregnancy could result in an afterload mismatch. This study examines LV size and function during vigorous stationary bicycle exercise performed in an erect position in 16 fit, pregnant women using 2-dimensional M-mode echocardiography.

Sixteen patients (aged 28 to 32 years [mean 30 ± 1], at a mean gestational age of 29 ± 6 weeks) exercised regularly before pregnancy and continued to exercise regularly during the entire pregnancy. The only medications received by these patients were prenatal vitamins. No patient admitted to smoking cigarettes. All patients were in normal sinus rhythm, and none had abnormal cardiac findings or abnormal ST segment at rest. No patient had any evidence of segmented LV abnormality. All patients gave written informed consent, approved by the institutional review board of University Hospitals of Cleveland, before the study. All patients were instructed to have a very light meal ≥2 hours before the exercise study. The temperature of the lab was maintained at approximately 70°F, with a relative humidity of 40 to 50% during the exercise period. Twelve-lead continuous electrocardiographic monitoring and blood pressure were recorded during the control period and at 2 minute intervals. Oxygen uptake, carbon dioxide production, respiratory exchange ratio, breathing frequency and tidal volume were determined from on-line analysis of inspired and expired gases at the mouth and within a mixing chamber measured by a mass spectrometer, together with expired volume.

Real-time data analysis was performed with a minicomputer and reported at 30-second intervals throughout the study. Maximum oxygen uptake was obtained by plotting the individual subject's attained heart rate and the measured oxygen uptake at the third minute of each work load, and extrapolating it to age-predicted maximal heart rate to obtain the maximal oxygen uptake. Maximal heart rate was expressed as oxygen uptake/ml/kg of body weight/min and as total. Functional aerobic capacity was calculated as follows: Percent functional aerobic capacity = (calculated maximal oxygen uptake/age–sex-predicted oxygen update) × 100. Fitness is related to the degree of functional aerobic capacity; very fit individuals achieve >100%. Left arm brachial blood pressure was obtained by auscultation. The fourth Korotkoff sound was used for diastolic values. All resting data were collected in the left lateral recumbent position and while at rest on the bicycle. Exercise was begun at 150 kg-m/min. Every 3 minutes into the exercise, work load intensity was increased by 150 kg-m/min. Patients continued to exercise until the target maternal heart rate was achieved (85% of age-predicted maximal heart rate) or until symptoms developed that precluded safe continuation of the test (dyspnea, leg cramps and fatigue). After exercise, patients recovered in the left lateral recumbent position until heart rate was within 10 beats/min of the pre-exercise heart rate obtained during the sitting position at rest, the respiratory exchange ratio was <1, or oxygen uptake was within 1 ml/kg · min of the pre-exercise value in the sitting position at rest. All fetuses were monitored before exercise and during recovery. Two-dimensional directed M-mode echocardiography was performed during the control period, at 2-minute mark intervals during each exercise stage and for 15 minutes during recovery. A 2.25 MHz transducer was used to obtain an LV view at the level of the chordae tendineae, as previously recommended by Popp et al.[3] The nadir of the septal endocardium, and the peak of the posterior wall were used for end-systolic dimension, as previously described.[2] All tracings were digitized using a digital image processing system (Digisonics, Houston, Texas). A maximum of 11 recordings per patient was obtained during the 3 periods. Volumes of the ventricle were determined using the formula described by Teicholz et al.[4] Analysis of variance was performed for repeated measures in the same subject. Statistical significance was determined between the resting values and the different exercise stages. Paired t test was used as appropriate. Results are expressed as mean ± SD. A p value <0.05 was considered statistically significant.

Fifteen of 16 patients exercised to ≥85% of the age-predicted maximal heart rate, and 1 had to stop before achieving the target rate, because she developed leg cramping and fatigue. Mean oxygen uptake was within 1.0 ml/kg · min (equal to product of heart rate, stroke volume and arteriovenous oxygen difference) and functional aerobic capacity were 25 ± 6 ml/kg/min and 89 ± 20%, respectively, indicating that the study cohort was fit. Three subjects were especially fit, as evidenced by a mean oxygen uptake of 39 ± 2 ml/kg · min, and a mean functional aerobic capacity of 124 ± 2%. All 16 subjects

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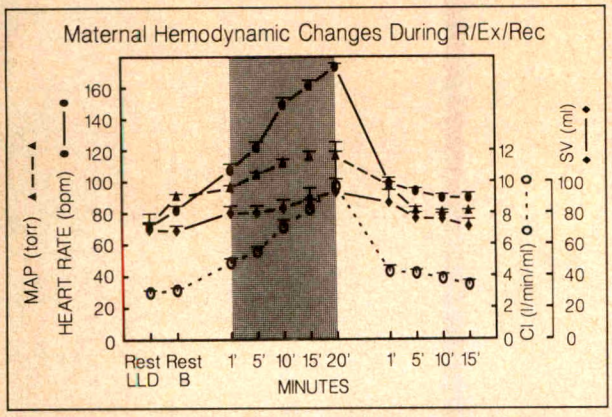


FIGURE 1. Hemodynamic values during rest (R), exercise (Ex) and recovery (Rec). Note that recovery data was obtained in left lateral decubitus (LLD) position. See text for results of significant changes. B = bicycle; CI = cardiac index; MAP = mean arterial pressure; SV = stroke volume.

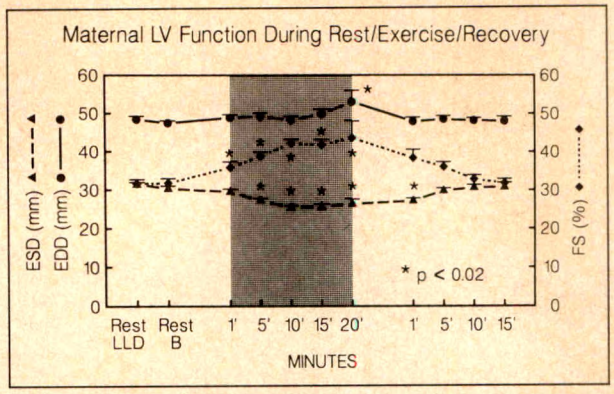


FIGURE 2. Left ventricular (LV) function during rest, exercise and recovery. End-diastolic dimensions (EDD) only increased significantly at the 20-minute mark of exercise. Percent change in fractional shortening (FS) significantly increased with exercise. End-systolic dimension (ESD) significantly decreased with exercise. Other abbreviations as in Figure 1.

exercised for ≥10 minutes, with 9 for 15 minutes, and 3 for 20 minutes. Heart rate and blood pressure significantly increased at the onset of exercise (Figure 1). Maximum mean blood pressure and heart rate increased significantly above resting values (116 ± 9 mm Hg and 173 ± 2 beats/min, respectively; Figure 1). No significant difference in LV end-diastolic dimension was found between the left lateral decubitus and the sitting position at rest. At the 20-minute mark, LV end-diastolic dimension significantly increased (53 ± 0.3 mm) over the baseline value at rest (48 ± 0.6 mm; p <0.01). LV end-systolic dimension decreased significantly during exercise (p <0.01), except during the first minute of exercise (Figure 2). At 5 minutes into recovery, LV end-systolic dimension returned to baseline value. Fractional shortening significantly increased with the onset of the exercise (36.5 ± 1% to 40.5 ± 1.5%; p <0.03) (Figure 2). It was still significantly increased at 10 minutes into recovery. Stroke volume and cardiac index increased rapidly with the onset of exercise and were still significantly increased 10 minutes into recovery (Figure 2). Fetal heart rates were monitored before and immediately before exercise, and at each minute into the recovery period using pulsed Doppler waveform of the umbilical artery. Fetal heart rate monitoring during exercise was technically difficult owing to maternal and fetal movements. In 73 fetal studies performed in these 16 subjects, a transient fetal bradycardia in its early recovery period was observed in only 3 cases. All fetal heart rates returned to baseline within 5 minutes after exercise. All patients (including the 3 aforementioned) delivered healthy term infants with good Apgar scores.[5]

Our study indicates that during vigorous bicycle ergometer exercise, LV function is maintained in the second half of pregnancy, despite great cardiovascular changes. The results also indicate that fit pregnant women can exercise at a high level of intensity without compromising LV function, that the left ventricle during pregnancy can still increase its dimension and output during strenuous exercise and that there is no decrease in stroke volume or cardiac index during the recovery period provided that subjects recovered in the lateral decubitus position. The 3 patients who were particularly fit may have biased the results, because there is a positive correlation between physical fitness and heart volume. The increase in LV end-diastolic dimension observed during high-intensity exercise in the 3 subjects with superior aerobic capacity (124%) indicates that the Frank-Starling mechanism is most likely operational in this group of pregnant women. We cannot extrapolate these results to less fit, but healthy, pregnant patients. M-mode echocardiography may have technical limitations. During exercise, excessive maternal breathing can occur. Chest wall motion due to increased ventilation can also cause significant artifact and impair visualization of the left ventricle. Changes in the heart axis occur during vigorous exercise and can affect the echocardiographic window. Despite these technical problems, the M-mode tracings obtained were of adequate quality for analysis. M-mode echocardiography is a reproducible and accurate method to assess LV size and function, provided that no segmental wall motion abnormalities, left bundle branch block nor pulmonary hypertension is present. None of our subjects had such complications. The Teichholz formula may not exactly apply to the pregnant heart. However, the significant increase in cardiac index found in these patients during exercise greatly exceeds any potential inherent error in this calculation. Fit pregnant patients can increase LV end-diastolic dimension during high-intensity exercise. No afterload mismatch occurred during exercise to cause deleterious affect on the LV function. Thus, despite the important normal cardiovascular adaptations that occur during pregnancy, LV size, contractility and stroke volume respond adequately to strenuous exercise. In this study, no reduction in stroke volume occurred in subjects during recovery. Although these subjects did not recover in the supine position, it would be advisable to continue the pumping action of the leg muscle during the cold down period to assure adequate venous return. In women who perform submaximal exercise and recover in a supine position, walking should be continued until maternal heart rate has returned to normal. To avoid poten-

tial fetal bradycardia, maximum maternal heart rate should be targeted at ≤148 beats/min.[6] The results of this study may not necessarily apply during either earlier or later gestation, or in a group of pregnant women who are not as fit as our patients (who were avid exercisers). Exercise at a high-intensity level may result in fetal bradycardia and should be performed only under supervision or in an exercise study protocol.

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Usefulness of Dynamic Hand Exercise for Developing Maximal Separation of Left and Right Ventricular Pressures at End-Diastole and Usefulness in Distinguishing Restrictive Cardiomyopathy from Constrictive Pericardial Disease

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Advances in differentiating restrictive cardiomyopathy from constrictive pericarditis has been gained by examining echocardiographic measures of diastolic function. Using Doppler echocardiography, Appleton et al[1] demonstrated an increase in right ventricular (RV) size and a concomitant decrease in left ventricular (LV) size during inspiration in patients with constriction. Using these same techniques, Hatle et al[2] showed opposite changes in inflow velocity across the mitral and tricuspid valves in patients with constrictive pericarditis but not restrictive cardiomyopathy. Despite these improvements in distinguishing restrictive cardiomyopathy from constrictive pericarditis in patients at rest, there have been few studies examining the effect of dynamic maneuvers on diastole as a means of distinguishing these 2 conditions.

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Manuscript received December 20, 1991; revised manuscript received January 24, 1992, and accepted January 28.

We addressed the hemodynamic differentiation of restrictive cardiomyopathy and constrictive pericarditis by evaluating the separation of LV and RV end-diastolic pressures after physiologic maneuvers. The traditional method for developing maximal separation of RV and LV end-diastolic pressures is rapid intravenous infusion of saline solution.[3] This method allows separation of end-diastolic pressures in patients with restrictive cardiomyopathy but not constrictive pericarditis.[3,4] Most patients with these disease states have elevated diastolic pressures, and a fluid challenge is potentially unsafe. Accordingly, we tested the hypothesis that dynamic hand exercise could provide a safe alternate means of maximizing the separation of LV and RV end-diastolic pressures in patients with restrictive cardiomyopathy but not constrictive pericarditis.

Twelve patients were enrolled in this study: 6 men, mean age 48 years, with atypical chest pain and normal left- and right-sided heart pressures, left ventriculography and coronary angiography were included in the normal group; 6 (3 men, mean age 54 years) with dys-

TABLE I Baseline Hemodynamics*

	No. of Pts.	RA	M Sign†	RV (s/d) (mm Hg)	Square Root Sign‡	PAW (mm Hg)	LV (s/d) (mm Hg)	Equalization of LVEDP and RVEDP§
Normal subjects	6	4	0	16/4	0	10	130/11	0
		3	0	20/5	0	5	120/10	0
		5	0	28/9	0	9	125/14	0
		7	0	22/8	0	7	115/13	0
		6	0	30/5	0	5	125/10	0
		8	0	22/8	0	6	135/12	0
Restriction	3	5	+	30/9	0	11	115/12	+
		32	+	65/26	+	34	120/28	+
		15	+	48/16	0	17	160/18	+
Constriction	3	14	+	36/14	0	14	120/15	+
		22	+	65/24	+	25	170/26	+
		24	+	86/24	+	35	120/25	+

*All pressures are in mm Hg.
†Prominent x and y descents on the RA pressure tracing.
‡On right ventricular pressure tracing.
§Equalization of LVEDP and RVEDP defined as <4 mm Hg separation.
LVEDP = left ventricular end-diastolic pressure; PAW = pulmonary artery wedge pressure; RA = right atrial pressure; RVEDP = right ventricular end-diastolic pressure; s/d = peak systole/end-diastole.

TABLE II Mean Separation of Left and Right Ventricular End-Diastolic Pressures*

	No. of Pts.	Baseline	VPC	Amyl Nitrite	Phase 4 Valsalva	Saline Infusion	DHE
Normal subjects	6	5 ± 1	4 ± 3	2 ± 3	8 ± 1†	10 ± 3†	13 ± 3†
Restriction	3	3 ± 2	1 ± 1	3 ± 2	3 ± 1	4 ± 1	5 ± 5
Constriction	3	1 ± 1	1 ± 1	2 ± 1	2 ± 1	2 ± 2	2 ± 2

*All pressures are in mm Hg.
†$p < 0.05$ versus baseline.
DHE = dynamic hand exercise; VPC = ventricular premature complexes.

pnea and a diagnosis of restrictive cardiomyopathy ($n = 3$) and constrictive pericarditis ($n = 3$) were included for evaluation. All patients were enrolled in accordance with the standards approved by the Human Investigations Committee of the University of Virginia.

All medications were withdrawn for 18 to 24 hours before cardiac catheterization. An interval of 15 minutes was required after contrast injection before the research protocol was initiated. RV pressures were measured with a no. 7Fr thermodilution Swan-Ganz catheter, and LV pressures with a no. 7Fr Gensini pigtail catheter. Venous and arterial pressures and electrocardiograms were recorded with a Honeywell Electronics for Medicine Recorder. Pressures were recorded on a 0 to 40 mm Hg scale at 50 mm/s and measured with fluid-filled transducers (Viggo-Spectramed, Oxnard, California).

Simultaneous LV and RV pressures were recorded at baseline, and during and immediately after each of 5 maneuvers designed to alter preload, afterload or contractility. Four of these 5 maneuvers (Valsalva, amyl nitrite, ventricular premature complexes and dynamic hand exercise) were performed in random order. Saline infusion was always performed as the fifth and final maneuver. After each maneuver, ventricular pressures were allowed to return to baseline.

1. To alter preload, the Valsalva maneuver was performed for a 10-second period and repeated once after a 1-minute interval of observation; and 1 liter of normal saline solution prewarmed to body temperature was infused over 10 minutes.

2. To alter afterload, amyl nitrite inhalation at nadir systolic pressure, and LV and RV end-diastolic pressures were recorded. This was followed by a 5-minute period of observation.

3. To alter contractility, 2 isolated ventricular premature complexes were induced with mechanical RV stimulation using the Swan-Ganz catheter, followed by a 1-minute period of observation; with the patient in the supine position, 2 blood pressure cuffs inflated to 40 mm Hg were placed in both hands, and the patient instructed to maximally inflate and release the blood pressure cuffs by grasping them simultaneously as quickly and forcibly as possible for a period of 3 minutes. All patients generated >75 mm Hg of pressure with each hand. Ventricular end-diastolic pressures were recorded at peak exercise. This was followed by a 5-minute period of observa-

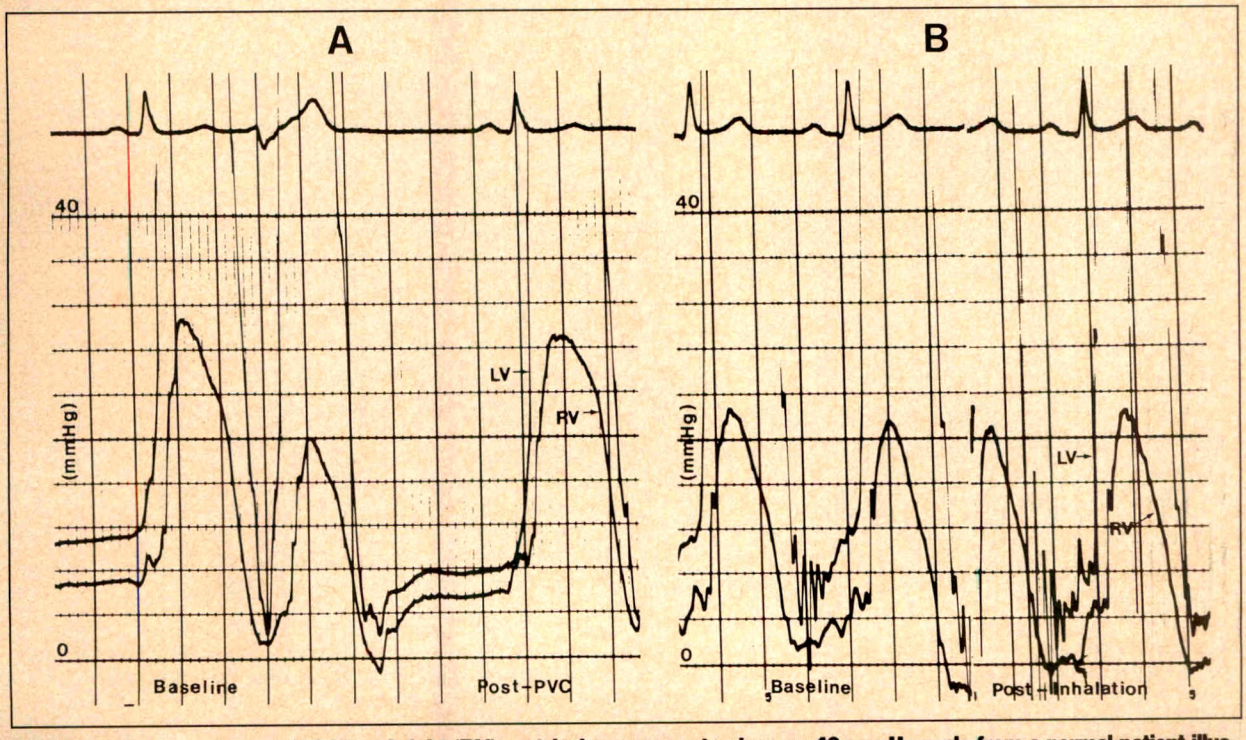


FIGURE 1. Representative left (LV) and right (RV) ventricular pressure tracings on 40 mm Hg scale from a normal patient illustrate the absence of separation of end-diastolic pressures after a single premature ventricular contraction *(A)* and after amyl nitrite inhalation *(B)*. In both cases, a greater decrease in LV than RV end-diastolic pressure occurs.

tion. Dynamic hand exercise is not isometric hand exercise.[5] The latter, during which sustained near-maximal hand pressure is maintained, was not examined in this study. Dynamic hand exercise was chosen in place of dynamic leg exercise due to the presence of femoral arterial and venous sheaths employed with the Judkins technique.

Maximal LV and RV end-diastolic pressure separation before and immediately after each maneuver was measured for 5 consecutive beats by 2 observers. End-diastole was defined as the peak of the R wave on the electrocardiogram. The following beats were analyzed: (1) the first beat after a ventricular premature complex; (2) 5 consecutive beats at nadir systolic pressure after amyl nitrite inhalation; (3) 5 consecutive beats during phase 4 of the Valsalva maneuver; (4) 5 consecutive beats at peak dynamic hand exercise; and (5) 5 consecutive beats immediately after saline infusion. Data reported are mean ± SD of these beats. Comparisons between end-diastolic pressure separation at baseline and imme-

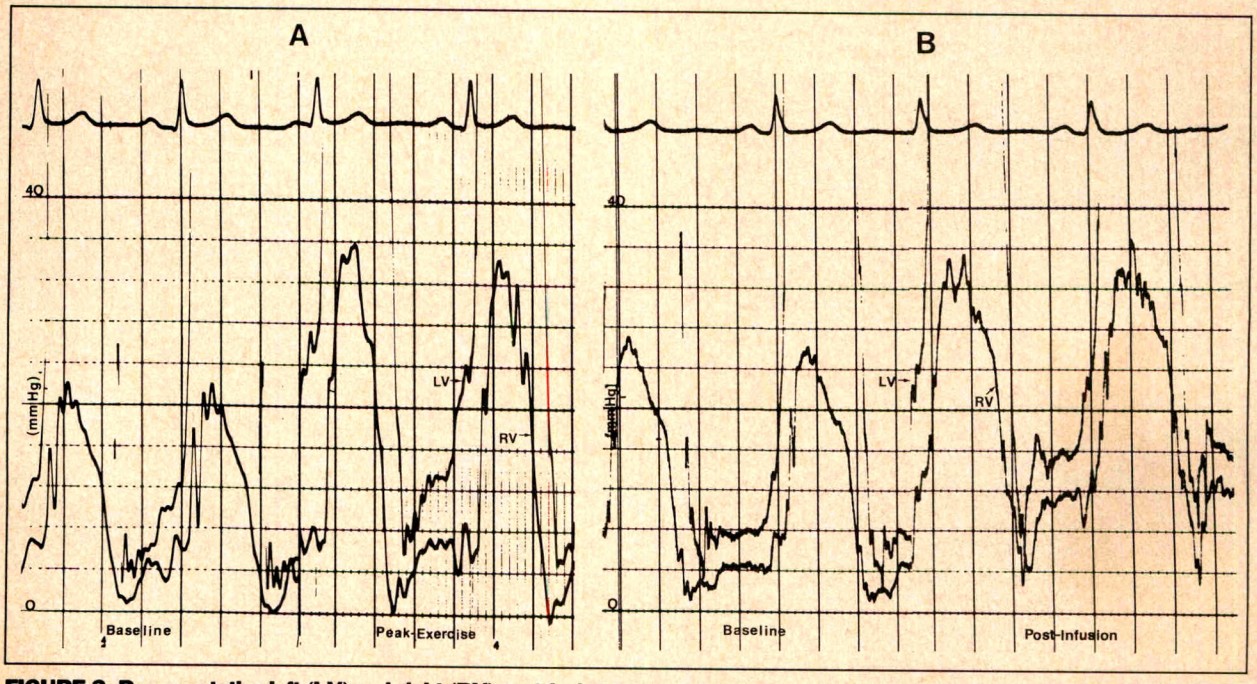


FIGURE 2. Representative left (LV) and right (RV) ventricular pressure tracings on 40 mm Hg scale obtained from a normal patient illustrate the change in end-diastolic pressure separation after dynamic hand exercise *(A)* and saline infusion *(B)*.

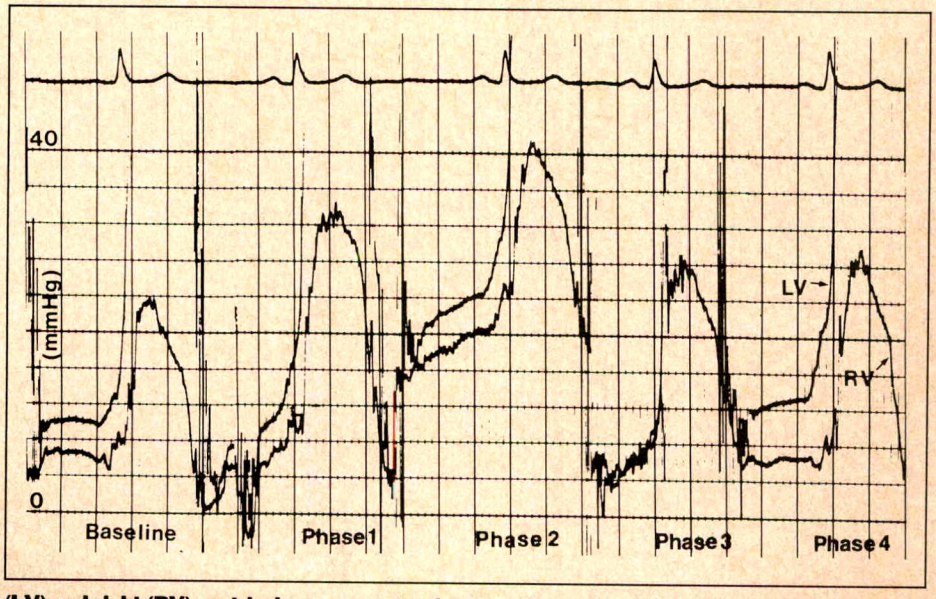


FIGURE 3. Left (LV) and right (RV) ventricular pressure tracings on 40 mm Hg scale obtained from representative single beats of a normal patient to illustrate the change in end-diastolic pressures during the 4 phases of a Valsalva maneuver. Initial increase in intrathoracic pressure is reflected in increasing LV and RV end-diastolic pressure (Phase 1 and Phase 2). Release of straining is followed immediately by a decrease in both ventricular pressures and a decreased separation of ventricular pressures at end-diastole (Phase 3). Reflex sympathetic increase in pressures then occurs and results in a greater increase in LV than RV end-diastolic pressure during the final phase of the maneuver (Phase 4), thus widening the separation of ventricular pressures at end-diastole.

diately after each maneuver were made using the Student's t *test.*

Baseline hemodynamics for the 2 patient groups studied are shown in Table I. In the normal group, filling pressures were normal, and all patients had ≥4 mm Hg separation of LV and RV end-diastolic pressures at baseline. For patients with restrictive or constrictive pathophysiology, filling pressures were elevated at baseline, except for 1 patient with restrictive cardiomyopathy. Patients with restrictive cardiomyopathy and constrictive pericarditis all had an "M" sign in the right atrial waveform, as well as equalization of LV and RV end-diastolic pressures, defined as <4 mm Hg separation at baseline.

Changes in mean LV and RV end-diastolic pressure separation in response to maneuvers for patient groups are summarized in Table II. In normal patients, both single ventricular premature complexes and amyl nitrite inhalation produced no separation of LV and RV end-diastolic pressures. Representative examples are shown in Figure 1. By contrast, separation of LV and RV end-diastolic pressures increased during phase 4 of the Valsalva maneuver, with saline infusion and with dynamic hand exercise in normal subjects. Representative tracings are shown in Figures 2 and 3. Mean separation of LV and RV end-diastolic pressures was not significant for patients with restrictive cardiomyopathy and constrictive pericarditis using any of these maneuvers.

Figure 3 displays representative beats reflecting changes in LV and RV end-diastolic pressures in a normal patient during the 4 phases of the Valsalva maneuver. An initial increase in both LV and RV end-diastolic pressures is seen during the first 2 phases of the maneuver. This is followed in phase 3 by a marked decrease in both LV and RV pressures, resulting in decreased separation of end-diastolic pressures. The maximal separation of LV and RV end-diastolic pressures is seen in phase 4 of the Valsalva maneuver when reflex sympathetic stimulation results in an increase in LV greater than RV end-diastolic pressure.

This study found that dynamic hand exercise and phase 4 of the Valsalva maneuver were as effective as saline infusion in producing maximal LV and RV end-diastolic pressure separation in normal patients. We prospectively applied these maneuvers to 6 patients with elevated and equal LV and RV end-diastolic pressures consistent with a diagnosis of restrictive cardiomyopathy or constrictive pericarditis. Separation of end-diastolic pressures did not occur in response to dynamic hand exercise, phase 4 of the Valsalva maneuver, or during saline infusion. These results disprove our original hypothesis that dynamic hand exercise could distinguish patients with restrictive cardiomyopathy from patients with constrictive pericarditis.

In both restrictive cardiomyopathy and constrictive pericarditis, baseline pressures at end-diastole are elevated and may be equal. In restrictive cardiomyopathy, the LV response to a hemodynamic maneuver should be independent of the right ventricle, since the pericardium, if normal, would not force the 2 ventricles to act as 1 and a noncompliant septum should not transmit pressures between the ventricles. By contrast, in constrictive pericarditis, the abnormal pericardium serves as a tight encasement coupling both ventricles. Elevation in left-sided heart pressures with a hemodynamic maneuver should be transmitted across a compliant septum and cause elevation in right-sided cardiac filling pressures. Therefore, in patients with equalization of end-diastolic pressures, a hemodynamic maneuver should separate LV and RV end-diastolic pressures in patients with restrictive cardiomyopathy, but not in those with constrictive pericarditis. This hypothesis was not confirmed probably because patients with constriction and restriction do not have pure involvement of either the myocardium or pericardium.

Dynamic hand exercise used in this study should be distinguished from isometric hand exercise.[5] Isometric hand exercise involves sustained isometric contraction of the forearm flexor muscles and produces a cardiovascular reflex. Isometric hand exercise, however, does not produce an increase in LV end-diastolic pressure[5] and thus would not be useful in increasing end-diastolic pressure separation in normal subjects as seen in this study.

In summary, although dynamic hand exercise can separate end-diastolic pressures in normal patients, it cannot be used to distinguish constrictive pericarditis from restrictive cardiomyopathy.

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Acute Myocardial Infarction Triggered by Emotional Stress

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Myocardial infarction has been shown to have a circadian pattern of occurrence, with a significantly increased incidence in the early morning hours.[1] Recognition that onset of acute coronary syndromes may not occur as a random event has led investigators to search for triggers of myocardial infarction.[2] Both psychological and physical stresses have been implicated as possible triggers. However, thus far only excessive physical exertion has been temporally linked to onset of pathologically documented acute myocardial infarction.[3] We report the first case of an acute myocardial infarction associated with extreme emotional upset, which resulted in cardiogenic shock and was successfully reversed by rapid treatment with thrombolytic therapy.

A 72-year-old Hispanic female smoker with diabetes mellitus presented to the emergency room at 11 P.M. with 2 hours of severe substernal chest pain that had begun 30 minutes after she was informed that her husband of 25 years had just died of a heart attack. She had not engaged in any strenuous physical activity that day. Physical examination was positive only for tachycardia and bibasilar rales. Initial electrocardiogram demonstrated sinus tachycardia with 1 mm ST elevation in lead V_2 and 1 mm ST depression in leads III and aVF. Chest pain resolved with nitrates, aspirin and oxygen. Twenty minutes later, the patient had recurrence of chest pain with the development of pulmonary edema and hypotension. Repeat electrocardiogram showed acute anterolateral ST elevations (Figure 1, top). The patient was treated with tissue-type plasminogen activator and heparin, with resolution of her chest pain and hypotension within 30 minutes. Continued respiratory distress necessitated intubation. An emergent echocardiogram revealed anterior akinesia with an estimated ejection fraction of 20 to 30%. She improved rapidly, and was extubated 12 hours after presentation. Repeat electrocardiogram revealed an evolving non-Q-wave acute myocardial infarction (Figure 1, bottom). Cardiac isoenzymes peaked 13 hours after thrombolysis at 606 U/liter. A repeat echocardiogram performed 48 hours after presentation revealed improvement of anterior and septal motion and overall mild left ventricular dysfunction. Because cardiogenic shock occurred in the setting of a small non-Q-wave myocardial infarction, it was presumed that there remained a significant amount of jeopardized myocardium and severe 3-vessel or left main coronary disease. Cardiac catheterization demonstrated calcific deposits and luminal irregularities (<30% diameter stenoses) in the proximal left anterior descending artery (Figure 2), without disease elsewhere in the coronary system and a normal left ventricle. The patient was discharged on aspirin and diltiazem, and has been without further symptoms at 8 months of follow-up.

This case demonstrates an association of acute psychological stress and acute myocardial infarction, and strongly suggests a triggering role. In addition, it proves that angiographically significant coronary disease need not be present, and that thrombolytic therapy can successful-

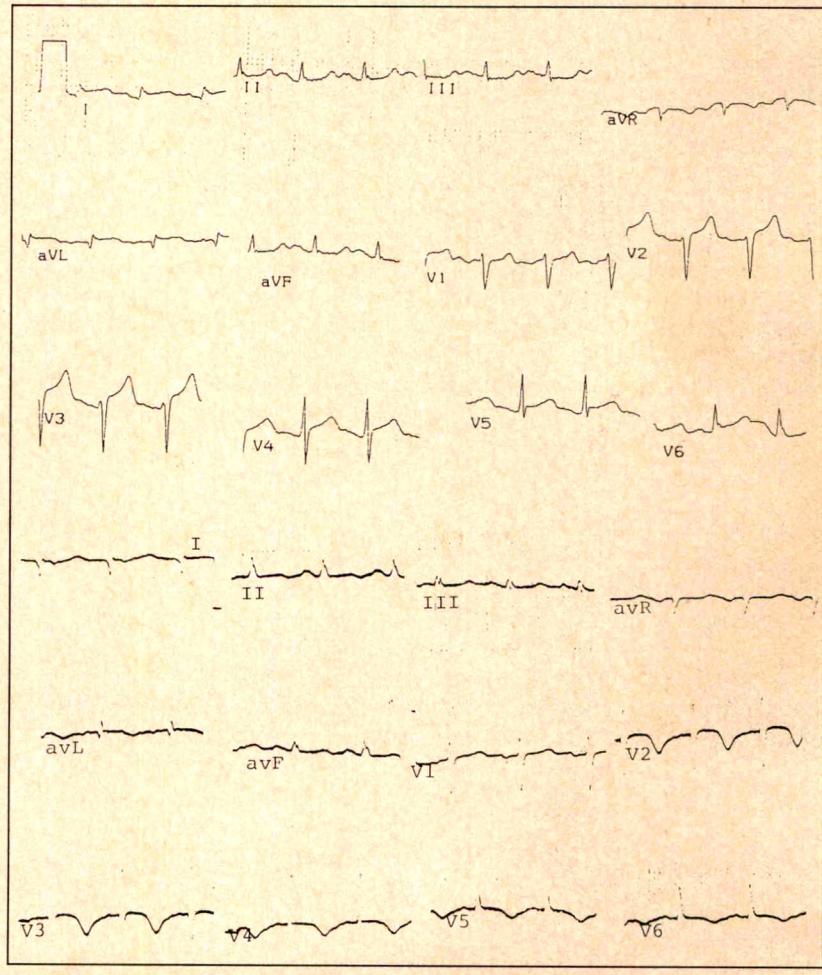


FIGURE 1. ***Top,*** **electrocardiogram demonstrating acute anterolateral wall myocardial infarction, with ST elevations V_2–V_6, I, aVL, and small R waves V_2–V_3.** ***Bottom,*** **repeat electrocardiogram after thrombolysis with normalization of ST elevations, return of R voltage in leads V_1–V_3, and inversion of T waves in leads V_2–V_6, I, aVL.**

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ly treat such a triggered infarct. We believe that this has important implications for the mechanisms by which triggers may act.

Extreme physical stress as a probable trigger of myocardial infarction has been described.[3] Investigators[4] have also demonstrated an association between mental stress and transient ischemia, and other workers[5] have reported an anecdotal association between various severe emotional stresses and sudden death. There are no prior reports of nonfatal myocardial infarction confirmed by enzymes with an unequivocal psychological trigger.

The absence of angiographically significant coronary disease in our patient is another unique feature of this case. It is increasingly recognized that an acute infarct will occur with rupture of a relatively "insignificant" plaque in which luminal narrowing has not reduced flow enough to cause symptoms.[6] In fact, plaque rupture may be more likely to occur in less angiographically significant lesions because such segments are more numerous, and perhaps because their lipid-to-fibrous tissue content is more conducive to rupture under appropriate physiologic conditions.[7] Studies identifying triggers in both nonfatal acute myocardial infarction[3] and sudden death[5] found significant coronary disease in at least 1 vessel in all patients.

We hypothesize that the acute stress of hearing that her husband died led to plaque rupture and subsequent thrombosis in the proximal left anterior descending artery of our patient. Coronary artery spasm is another possibility, but is less likely because improvement followed thrombolysis without antivasospastic therapy. A catecholamine surge, as evidenced by the patient's initial tachycardia, before shock, and out of proportion to her hemodynamic compromise, was probably an important contributor to the onset of infarction, although the infarct itself may have caused the catecholamine release. Mental stress has been shown to increase myocardial oxygen demand, heart rate and blood pressure, mediated at least in part by catecholamine secretion.[2] Coronary vascular resistance increases with mental stress in the presence of underlying coronary disease,[2] and this effect is seen with even minimal disease angiographically.[6] Emotional stress also increases platelet aggregation, at least in part by sympathoadrenal stimulation.[8] Thus, severe psychological stress can create an appropriate physiologic milieu in which plaque rupture and consequent thrombosis are more likely to occur. This case demonstrates that acute myocardial infarction and cardiogenic shock can be associated with and probably precipitated by acute psychological stress.

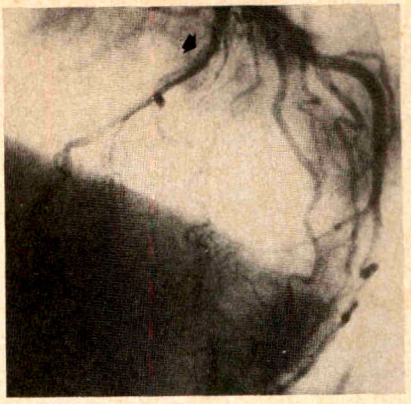


FIGURE 2. Coronary arteriogram of the left coronary system in the left anterior oblique projection. The vessels are widely patent, with a minor (<30%) stenosis in the proximal left anterior descending artery (*arrow*).

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Origin of the Right Coronary Artery from the Pulmonary Trunk

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Anomalous pulmonary origin of the right coronary artery (RCA) is a rare congenital cardiac malformation. Whereas patients with anomalous pulmonary origin of the left main coronary artery often present in infancy with signs of left ventricular ischemia or congestive heart failure, or both, those with anomalous origin of the RCA are usually asymptomatic. We have observed 2 patients with anomalous origin of the RCA at Children's Hospital Medical Center of Akron.

Case 1: A 4-year-old boy presented with a fever of 41°, and acute respiratory distress, and within 1 hour had cardiorespiratory arrest and died. He had been examined in 1969 at the age of 4 months for congestive heart failure and was erroneously diagnosed to have a large ventricular septal defect. He was then lost to follow-up until the terminal event. Autopsy showed aortopulmonary window and anomalous origin of the RCA from the pulmonary artery (Figure 1) with histologic changes compatible with advanced pulmonary vascular disease.

Case 2: A 5-year-old asymptomatic boy was referred because of a heart murmur. On physical examination, a grade 3/6 systolic murmur was noted, which was widely transmitted over the precordium. Electrocardiogram, chest x-ray and stress test were normal. An echocardio-

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Manuscript received September 20, 1991; revised manuscript received and accepted February 10, 1992.

gram with Doppler examination and color flow imaging showed a tiny paramembranous ventricular septal defect, a subaortic membrane with minimal gradient by Doppler, and strongly suggested anomalous origin of the RCA from the pulmonary trunk. Combined right- and left-sided cardiac catheterization study showed normal pressures and oxygen saturations. An aortic root cineangiogram showed a large left main coronary artery in the left sinus of Valsalva, no RCA in the aorta, and subsequent opacification of the RCA, which drained into the pulmonary trunk (Figure 2). Surgery has been recommended.

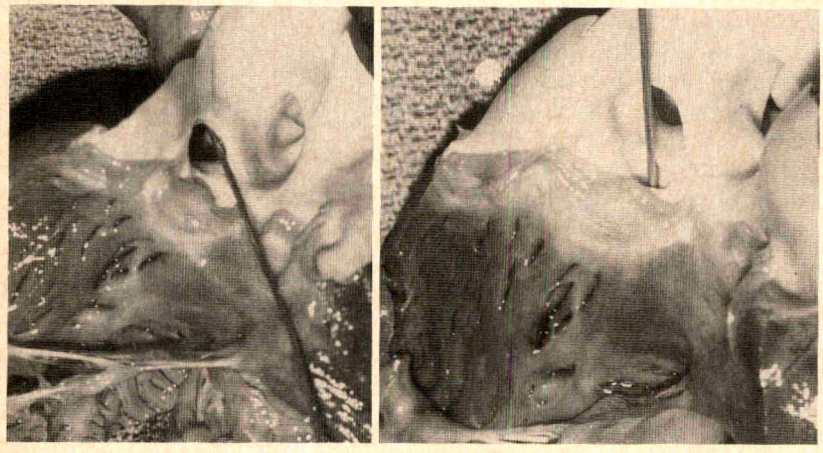


FIGURE 1. *Left,* heart with right ventricle and pulmonary artery opened to show aortopulmonary window *(probe). Right,* heart with right ventricle and pulmonary artery opened to show right coronary ostium in the pulmonary artery *(probe).*

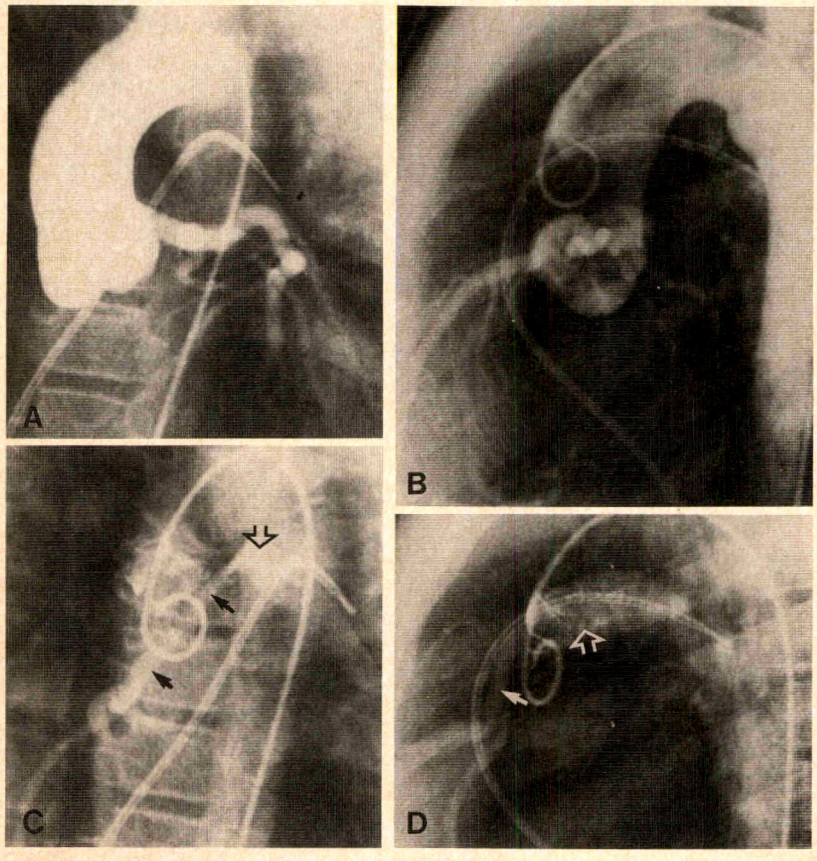


FIGURE 2. Aortic root angiogram. Anteroposterior *(A)* and lateral *(B)* views of early phase showing large left main coronary artery; right coronary artery is not seen. Note catheter in pulmonary artery. Anteroposterior *(C)* and lateral *(D)* views of late phase showing right coronary artery *(arrows)* emptying into pulmonary trunk *(open arrow).*

Since the first report of anomalous origin of the RCA from the pulmonary artery in 1885 by Sir John Brooks, 28 cases with angiographic or autopsy diagnosis have been reported.[1-6] Nine cases had associated congenital heart disease: tetralogy of Fallot (n = 3), aortopulmonary window (n = 3), atrial septal defect (n = 1), pulmonic stenosis (n = 1) and pulmonic atresia with intact ventricular septum (n = 1). The ages of the patients ranged from 17 hours to 90 years. Most patients with isolated anomalous origin of the RCA were asymptomatic. Four patients had symptoms or death attributed to the anomaly: 2 (aged 11 and 25 years, respectively) had cardiopulmonary arrest, a 2-year-old died suddenly, and a 47-year-old had angina pectoris.

Of the 4 types of anomalous origin of the coronary arteries from the pulmonary trunk, which have been described (anomalous origin of the left coronary artery, RCA, both coronary arteries and an accessory coronary artery), that of the RCA is the second most frequent anomaly.[3] The direction of flow is usually retrograde from the RCA into the pulmonary trunk.[3] The RCA is thin, dilated and vein-like, despite showing an arterial structure histologically.[3] After the diagnosis is obtained, direct implantation of the RCA into the aorta is recommended.[4] Diagnosis can be obtained (or strongly suspected) on echocardiographic examination with color flow imaging.[5,6]

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Richard Lower: Complete Physician — Scientist–Pericardiologist

Appropriately lauded as "a pioneer of cardiologic research,"[1] the 17th century's Richard Lower was equally accomplished in clinical observation and clinicopathologic correlation, appreciation of which helps to complete any professional portrait. He observed pulsus paradoxus, noting "the intermission itself of the pulse" to constantly follow each inspiration and described a 30-year-old woman with pericardial disease with progressive breathlessness, fainting, weakness and feeble, "intermittent" pulse, who at autopsy had advanced pericardial fibrosis with diaphragmatic adhesions.[2] Lower ascribed the "intermittent" (modern: "paradoxic") pulse to these. This was certainly consistent with the contemporary static pathology and, rightly or wrongly, anticipated Dock's explanation of inspiratory diaphragmatic traction[3] by some 200 years—an astute clinician made more astute by physiologic deduction from clinicopathologic correlation. Indeed, since "pulsus paradoxus" is not paradoxic, Lower's "intermittent pulse" has the virtue, at least, of being descriptive and not erroneous.[4]

Especially striking are Lower's concepts of pericardial constriction:

"With regard to this, the covering of the Heart, let it be said, it cannot have its function described by one term, for it serves to keep the Heart moist to protect it from external injuries; . . . when too much water accumulates in it, injury of the Heart results and when (fluid) is lacking, it adheres closely to the Heart, even on all sides to it; since it also is attached to the diaphragm it is inevitable that the motion of the Heart is combined and united with it . . . this must be regarded as a great impediment and inconvenience. . . ."[5] and of cardiac tamponade:

"Just as the heart labors when affected by disease within, so it does when oppressed from without by disease of its covering. So it happens when that same covering of the Heart is filled with an effusion, and the walls are compressed with water on every side, so that they *cannot dilate* [italics mine—D.H.S.]; then truly the pulse diminishes until at length it is suppressed by even more water, when syncope, and death itself follows. Just as the accumulation of too much water harms the heart, so too does trouble come when the heart and the pericardium become everywhere adherent. . . ."[5] Although neither Dock's nor Lower's quite reasonable diaphragmatic traction hypotheses have been rigorously supported,[6] these perspicacious observations on the impact of each form of cardiac compression anticipated by 200 years what contemporary physiologists and clinical physiologists have elegantly established: pericardial constraint of the heart is due to *diastolic* dysfunction,[6] a matter of some uncertainty until comparatively recently. Indeed, Richard Lower, mirrored by current "pericardiologists" long ago anticipated the comparatively recent awakening of the majority of cardiologic clinicians and investigators to the significance of diastole.

David H. Spodick, MD, DSc
Worcester, Massachusetts
2 March 1992

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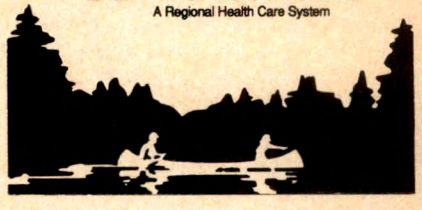
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HYPOMAGNESEMIA, MAGNESIUM DEFICIENCIES and/or MAGNESIUM DEPLETION *resulting from diuretic and/or digitalis therapy*[1], alcoholism[2], Cisplatin[3], Amphotericin B[4], Cyclosporin[5], perenteral nutrition[6], mannitol[7], Aminoglycosides[8], and diets low in Magnesium.

Note: May aid in preventing Calcium Oxaluria

SYMPTOMS: Refractory Hypokalemia, Tremors, and cramping of extremities and tongue, grimaces, myoclonic jerks, Chvostek's sign, ataxia, irritability, disorientation, convulsion, psychotic behavior.

CAUTION: Magnesium should be used with caution in renal insufficiency. If aperient, reduce dosage.

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Lopressor®
metoprolol tartrate USP

Tablets
Ampuls

BRIEF SUMMARY (FOR FULL PRESCRIBING INFORMATION, SEE PACKAGE INSERT)

INDICATIONS AND USAGE
Hypertension
Lopressor tablets are indicated for the treatment of hypertension. They may be used alone or in combination with other antihypertensive agents.

Angina Pectoris
Lopressor is indicated in the long-term treatment of angina pectoris.

Myocardial Infarction
Lopressor ampuls and tablets are indicated in the treatment of hemodynamically stable patients with definite or suspected acute myocardial infarction to reduce cardiovascular mortality. Treatment with intravenous Lopressor can be initiated as soon as the patient's clinical condition allows (see **DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS,** and **WARNINGS**). Alternatively, treatment can begin within 3 to 10 days of the acute event (see **DOSAGE AND ADMINISTRATION**).

CONTRAINDICATIONS
Hypertension and Angina
Lopressor is contraindicated in sinus bradycardia, heart block greater than first degree, cardiogenic shock, and overt cardiac failure (see **WARNINGS**).

Myocardial Infarction
Lopressor is contraindicated in patients with a heart rate < 45 beats/min; second- and third-degree heart block; significant first-degree heart block (P-R interval ≥ 0.24 sec); systolic blood pressure < 100 mmHg; or moderate-to-severe cardiac failure (see **WARNINGS**).

WARNINGS
Hypertension and Angina
Cardiac Failure: Sympathetic stimulation is a vital component supporting circulatory function in congestive heart failure, and beta blockade carries the potential hazard of further depressing myocardial contractility and precipitating more severe failure. In hypertensive and angina patients who have congestive heart failure controlled by digitalis and diuretics, Lopressor should be administered cautiously. Both digitalis and Lopressor slow AV conduction.

In Patients Without a History of Cardiac Failure: Continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or given a diuretic. The response should be observed closely. If cardiac failure continues, despite adequate digitalization and diuretic therapy, Lopressor should be withdrawn.

Ischemic Heart Disease: Following abrupt cessation of therapy with certain beta-blocking agents, exacerbations of angina pectoris and, in some cases, myocardial infarction have occurred. When discontinuing chronically administered Lopressor, particularly in patients with ischemic heart disease, the dosage should be gradually reduced over a period of 1-2 weeks and the patient should be carefully monitored. If angina markedly worsens or acute coronary insufficiency develops, Lopressor administration should be reinstated promptly, at least temporarily, and other measures appropriate for the management of unstable angina should be taken. Patients should be warned against interruption or discontinuation of therapy without the physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue Lopressor therapy abruptly even in patients treated only for hypertension.

Bronchospastic Diseases: **PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD, IN GENERAL, NOT RECEIVE BETA BLOCKERS. Because of its relative beta$_1$ selectivity, however, Lopressor may be used with caution in patients with bronchospastic disease who do not respond to, or cannot tolerate, other antihypertensive treatment. Since beta$_1$ selectivity is not absolute, a beta$_2$-stimulating agent should be administered concomitantly, and the lowest possible dose of Lopressor should be used. In these circumstances it would be prudent initially to administer Lopressor in smaller doses three times daily, instead of larger doses two times daily, to avoid the higher plasma levels associated with the longer dosing interval. (See DOSAGE AND ADMINISTRATION.)**

Major Surgery: The necessity or desirability of withdrawing beta-blocking therapy prior to major surgery is controversial; the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures.

Lopressor, like other beta blockers, is a competitive inhibitor of beta-receptor agonists, and its effects can be reversed by administration of such agents, e.g., dobutamine or isoproterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in restarting and maintaining the heart beat has also been reported with beta blockers.

Diabetes and Hypoglycemia: Lopressor should be used with caution in diabetic patients if a beta-blocking agent is required. Beta blockers may mask tachycardia occurring with hypoglycemia, but other manifestations such as dizziness and sweating may not be significantly affected.

Thyrotoxicosis: Beta-adrenergic blockade may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. Patients suspected of developing thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of beta blockade, which might precipitate a thyroid storm.

Myocardial Infarction
Cardiac Failure: Sympathetic stimulation is a vital component supporting circulatory function, and beta blockade carries the potential hazard of depressing myocardial contractility and precipitating or exacerbating minimal cardiac failure.

During treatment with Lopressor, the hemodynamic status of the patient should be carefully monitored. If heart failure occurs or persists despite appropriate treatment, Lopressor should be discontinued.

Bradycardia: Lopressor produces a decrease in sinus heart rate in most patients; this decrease is greatest among patients with high initial heart rates and least among patients with low initial heart rates. Acute myocardial infarction (particularly inferior infarction) may in itself produce significant lowering of the sinus rate. If the sinus rate decreases to < 40 beats/min, particularly if associated with evidence of lowered cardiac output, atropine (0.25-0.5 mg) should be administered intravenously. If treatment with atropine is not successful, Lopressor should be discontinued, and cautious administration of isoproterenol or installation of a cardiac pacemaker should be considered.

AV Block: Lopressor slows AV conduction and may produce significant first- (P-R interval ≥0.26 sec), second-, or third-degree heart block. Acute myocardial infarction also produces heart block.

If heart block occurs, Lopressor should be discontinued and atropine (0.25-0.5 mg) should be administered intravenously. If treatment with atropine is not successful, cautious administration of isoproterenol or installation of a cardiac pacemaker should be considered.

Hypotension: If hypotension (systolic blood pressure ≤ 90 mmHg) occurs, Lopressor should be discontinued, and the hemodynamic status of the patient and the extent of myocardial damage carefully assessed. Invasive monitoring of central venous, pulmonary capillary wedge, and arterial pressures may be required. Appropriate therapy with fluids, positive inotropic agents, balloon counterpulsation, or other treatment modalities should be instituted. If hypotension is associated with sinus bradycardia or AV block, treatment should be directed at reversing these (see above).

Bronchospastic Diseases: **PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD, IN GENERAL, NOT RECEIVE BETA BLOCKERS. Because of its relative beta$_1$ selectivity, Lopressor may be used with extreme caution in patients with bronchospastic disease. Because it is unknown to what extent beta$_2$-stimulating agents may exacerbate myocardial ischemia and the extent of infarction, these agents should *not* be used prophylactically. If bronchospasm not related to congestive heart failure occurs, Lopressor should be discontinued. A theophylline derivative or a beta$_2$ agonist may be administered cautiously, depending on the clinical condition of the patient. Both theophylline derivatives and beta$_2$ agonists may produce serious cardiac arrhythmias.**

PRECAUTIONS
General
Lopressor should be used with caution in patients with impaired hepatic function.

Information for Patients
Patients should be advised to take Lopressor regularly and continuously, as directed, with or immediately following meals. If a dose should be missed, the patient should take only the next scheduled dose (without doubling it). Patients should not discontinue Lopressor without consulting the physician.

Patients should be advised (1) to avoid operating automobiles and machinery or engaging in other tasks requiring alertness until the patient's response to therapy with Lopressor has been determined; (2) to contact the physician if any difficulty in breathing occurs; (3) to inform the physician or dentist before any type of surgery that he or she is taking Lopressor.

Laboratory Tests
Clinical laboratory findings may include elevated levels of serum transaminase, alkaline phosphatase, and lactate dehydrogenase.

Drug Interactions
Catecholamine-depleting drugs (e.g., reserpine) may have an additive effect when given with beta-blocking agents. Patients treated with Lopressor plus a catecholamine depletor should therefore be closely observed for evidence of hypotension or marked bradycardia, which may produce vertigo, syncope, or postural hypotension.

Risk of Anaphylactic Reaction. While taking beta-blockers, patients with a history of severe anaphylactic reaction to a variety of allergens may be more reactive to repeated challenge, either accidental, diagnostic, or therapeutic. Such patients may be unresponsive to the usual doses of epinephrine used to treat allergic reaction.

Carcinogenesis, Mutagenesis, Impairment of Fertility
Long-term studies in animals have been conducted to evaluate carcinogenic potential. In a 2-year study in rats at three oral dosage levels of up to 800 mg/kg per day, there was no increase in the development of spontaneously occurring benign or malignant neoplasms of any type. The only histologic changes that appeared to be drug related were an increased incidence of generally mild focal accumulation of foamy macrophages in pulmonary alveoli and a slight increase in biliary hyperplasia. In a 21-month study in Swiss albino mice at three oral dosage levels of up to 750 mg/kg per day, benign lung tumors (small adenomas) occurred more frequently in female mice receiving the highest dose than in untreated control animals. There was no increase in malignant or total (benign plus malignant) lung tumors, nor in the overall incidence of tumors or malignant tumors. This 21-month study was repeated in CD-1 mice, and no statistically or biologically significant differences were observed between treated and control mice of either sex for any type of tumor.

All mutagenicity tests performed (a dominant lethal study in mice, chromosome studies in somatic cells, a Salmonella/mammalian-microsome mutagenicity test, and a nucleus anomaly test in somatic interphase nuclei) were negative.

No evidence of impaired fertility due to Lopressor was observed in a study performed in rats at doses up to 55.5 times the maximum daily human dose of 450 mg.

Pregnancy Category C
Lopressor has been shown to increase postimplantation loss and decrease neonatal survival in rats at doses up to 55.5 times the maximum daily human dose of 450 mg. Distribution studies in mice confirm exposure of the fetus when Lopressor is administered to the pregnant animal. These studies have revealed no evidence of impaired fertility or teratogenicity. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers
Lopressor is excreted in breast milk in very small quantity. An infant consuming 1 liter of breast milk daily would receive a dose of less than 1 mg of the drug. Caution should be exercised when Lopressor is administered to a nursing woman.

Pediatric Use
Safety and effectiveness in children have not been established.

ADVERSE REACTIONS
Hypertension and Angina
Most adverse effects have been mild and transient.

Central Nervous System: Tiredness and dizziness have occurred in about 10 of 100 patients. Depression has been reported in about 5 of 100 patients. Mental confusion and short-term memory loss have been reported. Headache, nightmares, and insomnia have also been reported.

Cardiovascular: Shortness of breath and bradycardia have occurred in approximately 3 of 100 patients. Cold extremities; arterial insufficiency, usually of the Raynaud type; palpitations; congestive heart failure; peripheral edema; and hypotension have been reported in about 1 of 100 patients. (See **CONTRAINDICATIONS, WARNINGS,** and **PRECAUTIONS**.)

Respiratory: Wheezing (bronchospasm) and dyspnea have been reported in about 1 of 100 patients (see **WARNINGS**).

Gastrointestinal: Diarrhea has occurred in about 5 of 100 patients. Nausea, dry mouth, gastric pain, constipation, flatulence, and heartburn have been reported in about 1 of 100 patients.

Hypersensitive Reactions: Pruritus or rash have occurred in about 5 of 100 patients. Worsening of psoriasis has also been reported.

Miscellaneous: Peyronie's disease has been reported in fewer than 1 of 100,000 patients. Musculoskeletal pain, blurred vision, and tinnitus have also been reported.

There have been rare reports of reversible alopecia, agranulocytosis, and dry eyes. Discontinuation of the drug should be considered if any such reaction is not otherwise explicable.

The oculomucocutaneous syndrome associated with the beta blocker practolol has not been reported with Lopressor.

Myocardial Infarction
Central Nervous System: Tiredness has been reported in about 1 of 100 patients. Vertigo, sleep disturbances, hallucinations, headache, dizziness, visual disturbances, confusion, and reduced libido have also been reported, but a drug relationship is not clear.

Cardiovascular: In the randomized comparison of Lopressor and placebo described in the **CLINICAL PHARMACOLOGY** section, the following adverse reactions were reported:

	Lopressor	*Placebo*
Hypotension (systolic BP < 90 mmHg)	27.4%	23.2%
Bradycardia (heart rate < 40 beats/min)	15.9%	6.7%
Second- or third-degree heart block	4.7%	4.7%
First-degree heart block (P-R ≥ 0.26 sec)	5.3%	1.9%
Heart failure	27.5%	29.6%

Respiratory: Dyspnea of pulmonary origin has been reported in fewer than 1 of 100 patients.

Gastrointestinal: Nausea and abdominal pain have been reported in fewer than 1 of 100 patients.

Dermatologic: Rash and worsened psoriasis have been reported, but a drug relationship is not clear.

Miscellaneous: Unstable diabetes and claudication have been reported, but a drug relationship is not clear.

Potential Adverse Reactions
A variety of adverse reactions not listed above have been reported with other beta-adrenergic blocking agents and should be considered potential adverse reactions to Lopressor.

Central Nervous System: Reversible mental depression progressing to catatonia; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.

Cardiovascular: Intensification of AV block (see **CONTRAINDICATIONS**).

Hematologic: Agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

Hypersensitive Reactions: Fever combined with aching and sore throat, laryngospasm, and respiratory distress.

OVERDOSAGE
Acute Toxicity
Several cases of overdosage have been reported, some leading to death.

Oral LD_{50}'s (mg/kg): mice, 1158-2460; rats, 3090-4670.

Signs and Symptoms
Potential signs and symptoms associated with overdosage with Lopressor are bradycardia, hypotension, bronchospasm, and cardiac failure.

Treatment
There is no specific antidote.

In general, patients with acute or recent myocardial infarction may be more hemodynamically unstable than other patients and should be treated accordingly (see **WARNINGS, Myocardial Infarction**).

On the basis of the pharmacologic actions of Lopressor, the following general measures should be employed:

Elimination of the Drug: Gastric lavage should be performed.

Bradycardia: Atropine should be administered. If there is no response to vagal blockade, isoproterenol should be administered cautiously.

Hypotension: A vasopressor should be administered, e.g., levarterenol or dopamine.

Bronchospasm: A beta$_2$-stimulating agent and/or a theophylline derivative should be administered.

Cardiac Failure: A digitalis glycoside and diuretic should be administered. In shock resulting from inadequate cardiac contractility, administration of dobutamine, isoproterenol, or glucagon may be considered.

Printed in U.S.A. C90-39 (Rev. 7/90)

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1. 1988 Joint National Committee. The 1988 report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure. *Arch Intern Med.* 1988;148:1023-1038.

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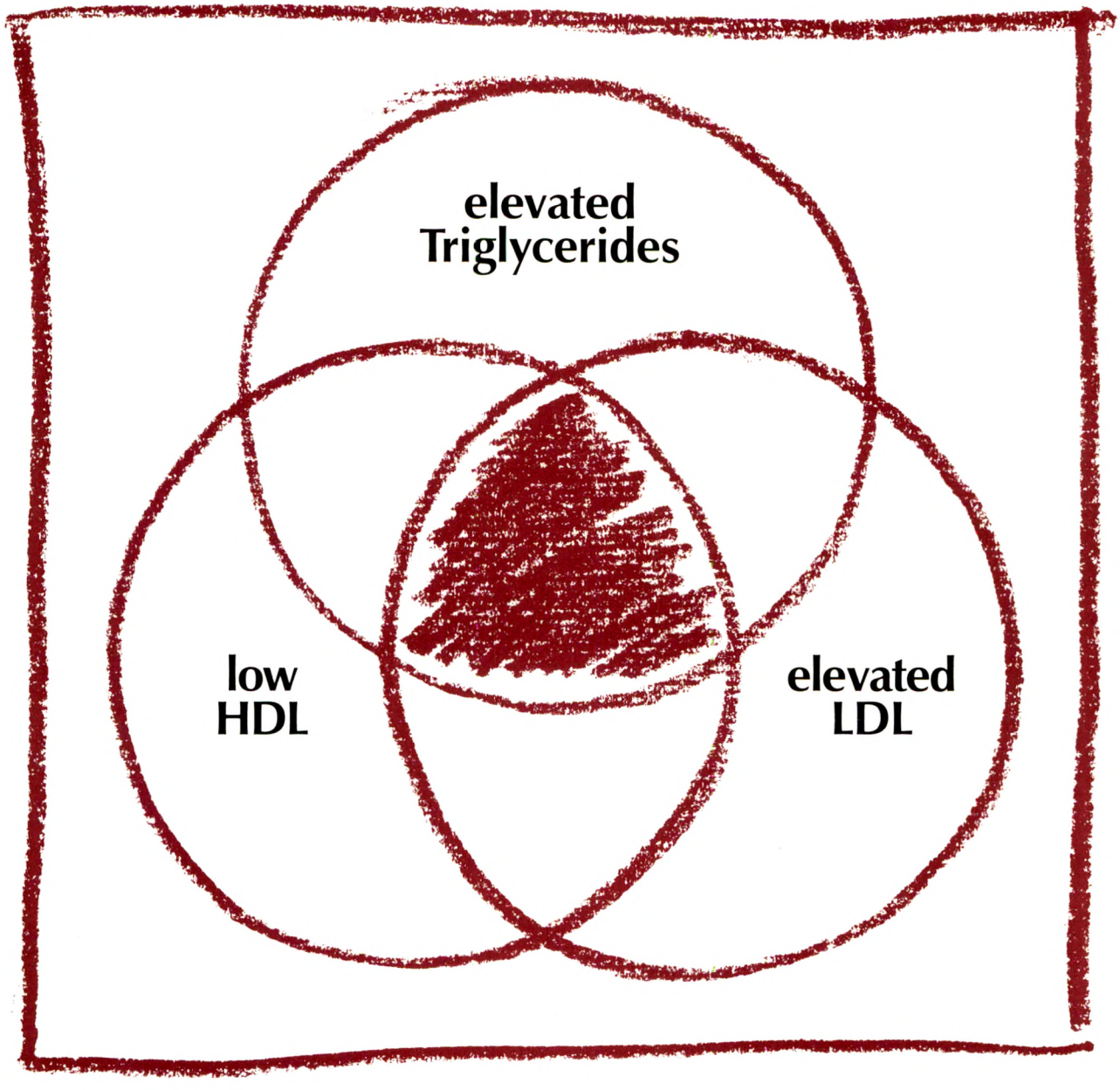
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Reduce the risk of developing CHD in patients with the triad of risk...



As an adjunct to diet, after an inadequate response to exercise, dietary therapy, weight loss and trial of other pharmacologic agents (such as bile acid sequestrants and nicotinic acid)

LOPID®

(*gemfibrozil*) 600-mg Tablets BID

REDUCES THE RISK OF DEVELOPING CHD
IN PATIENTS WITH THE TRIAD OF RISK

LOPID is indicated as adjunctive therapy to diet for reducing the risk of developing coronary heart disease **only** in Type IIb patients:

- Without history of or symptoms of existing coronary heart disease
- Who have had an inadequate response to weight loss, dietary therapy, exercise, and other pharmacologic agents (such as bile acid sequestrants and nicotinic acid, known to reduce LDL- and raise HDL-cholesterol)

and

- Who have the following triad of lipid abnormalities: low HDL-cholesterol levels in addition to elevated LDL-cholesterol and elevated triglycerides

In addition:

- The potential benefit of gemfibrozil in treating Type IIa patients with elevations of LDL-cholesterol only is not likely to outweigh the risks
- LOPID is not indicated for the treatment of patients with low HDL-cholesterol as their only lipid abnormality

LOPID is contraindicated in patients with hepatic or severe renal dysfunction, including primary biliary cirrhosis, preexisting gallbladder disease, or hypersensitivity to gemfibrozil

LOPID may increase cholesterol secretion into the bile, leading to cholelithiasis

Caution should be exercised when anticoagulants are given in conjunction with LOPID

Please see last page of this advertisement for brief summary of prescribing information.

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BOOTS PHARMACEUTICALS

PARKE-DAVIS Division of Warner-Lambert Company, Morris Plains, New Jersey 07950



Before prescribing, please see full prescribing information. A Brief Summary follows.

CONTRAINDICATIONS

1. Hepatic or severe renal dysfunction, including primary biliary cirrhosis.
2. Preexisting gallbladder disease (see WARNINGS).
3. Hypersensitivity to gemfibrozil.

WARNINGS

1. Because of chemical, pharmacological, and clinical similarities between gemfibrozil and clofibrate, the adverse findings with clofibrate in two large clinical studies may also apply to gemfibrozil. In the first of those studies, the Coronary Drug Project, 1000 subjects with previous myocardial infarction were treated for five years with clofibrate. There was no difference in mortality between the clofibrate-treated subjects and 3000 placebo-treated subjects, but twice as many clofibrate-treated subjects developed cholelithiasis and cholecystitis requiring surgery. In the other study, conducted by the World Health Organization (WHO), 5000 subjects without known coronary heart disease were treated with clofibrate for five years and followed one year beyond. There was a statistically significant, 44%, higher age-adjusted total mortality in the clofibrate-treated than in a comparable placebo-treated control group during the trial period. The excess mortality was due to a 33% increase in noncardiovascular causes, including malignancy, post-cholecystectomy complications, and pancreatitis. The higher risk of clofibrate-treated subjects for gallbladder disease was confirmed.

Because of the more limited size of the Helsinki Heart Study, the observed difference in mortality from any cause between the Lopid and placebo group is not statistically significantly different from the 29% excess mortality reported in the clofibrate group in the separate WHO study at the 9 year follow-up. Noncoronary heart disease related mortality showed an excess in the group originally randomized to Lopid primarily due to cancer deaths observed during the open-label extension.

During the 5 year primary prevention component of the Helsinki Heart Study mortality from any cause was 44 (2.2%) in the Lopid group and 43 (2.1%) in the placebo group; including the 3.5 year follow-up period since the trial was completed, cumulative mortality from any cause was 101 (4.9%) in the Lopid group and 83 (4.1%) in the group originally randomized to placebo (hazard ratio 1.20 in favor of placebo). Because of the more limited size of the Helsinki Heart Study, the observed difference in mortality from any cause between the Lopid and placebo groups at year-5 or at year-8.5 is not statistically significantly different from the 29% excess mortality reported in the clofibrate group in the separate WHO study at the 9 year follow-up. Noncoronary heart disease related mortality showed an excess in the group originally randomized to Lopid at the 8.5 year follow-up (65 Lopid versus 45 placebo noncoronary deaths).

The incidence of cancer (excluding basal cell carcinoma) discovered during the trial and in the 3.5 years after the trial was completed was 51 (2.5%) in both originally randomized groups. In addition, there were 16 basal cell carcinomas in the group originally randomized to Lopid and 9 in the group originally randomized to placebo ($p = 0.22$). There were 30 (1.5%) deaths attributed to cancer in the group originally randomized to Lopid and 18 (0.9%) in the group originally randomized to placebo ($p = 0.11$). Adverse outcomes, including coronary events, were higher in gemfibrozil patients in a corresponding study in men with a history of known or suspected coronary heart disease in the secondary prevention component of the Helsinki Heart Study. See CLINICAL PHARMACOLOGY section in full prescribing information which includes the following: The secondary prevention component of the Helskinki Heart Study was conducted over 5 years in parallel and at the same centers in Finland in 628 middle-aged males excluded from the primary prevention component of the Helsinki Heart Study because of a history of angina, myocardial infarction or unexplained ECG changes. The primary efficacy endpoint of the study was cardiac events (the sum of fatal and non-fatal myocardial infarctions and sudden cardiac deaths). The hazard ratio (Lopid:placebo) for cardiac events was 1.47 (95% confidence limits 0.88-2.48, p=0.14). Of the 35 patients in the Lopid group who experienced cardiac events, 12 patients suffered events after discontinuation from the study. Of the 24 patients in the placebo group with cardiac events, 4 patients suffered events after discontinuation from the study. There were 17 cardiac deaths in the Lopid group and 8 in the placebo group (hazard ratio 2.18; 95% confidence limits 0.94-5.05, p=0.06). Ten of these deaths in the Lopid group and 3 in the placebo group occurred after discontinuation from therapy. In this study of patients with known or suspected coronary heart disease, no benefit from Lopid treatment was observed in reducing cardiac events or cardiac deaths. Thus, Lopid has shown benefit only in selected dyslipidemic patients *without* suspected or established coronary heart disease. Even in patients with coronary heart disease and the triad of elevated LDL-cholesterol, elevated triglycerides, plus low HDL-cholesterol, the possible effect of Lopid on coronary events has not been adequately studied.

2. A gallstone prevalence substudy of 450 Helsinki Heart Study participants showed a trend toward a greater prevalence of gallstones during the study within the Lopid treatment group (7.5% vs 4.9% for the placebo group, a 55% excess for the gemfibrozil group). A trend toward a greater incidence of gallbladder surgery was observed for the Lopid group (17 vs 11 subjects, a 54% excess). This result did not differ statistically from the increased incidence of cholecystectomy observed in the WHO study in the group treated with clofibrate. Both clofibrate and gemfibrozil may increase cholesterol excretion into the bile leading to cholelithiasis. If cholelithiasis is suspected, gallbladder studies are indicated. Lopid therapy should be discontinued if gallstones are found.

3. Since a reduction of mortality from coronary heart disease has not been demonstrated and because liver and interstitial cell testicular tumors were increased in rats, Lopid should be administered only to those patients described in the INDICATIONS AND USAGE section. If a significant serum lipid response is not obtained, Lopid should be discontinued.

4. Concomitant Anticoagulants – Caution should be exercised when anticoagulants are given in conjunction with Lopid. The dosage of the anticoagulant should be reduced to maintain the prothrombin time at the desired level to prevent bleeding complications. Frequent prothrombin determinations are advisable until it has been definitely determined that the prothrombin level has stabilized.

5. Concomitant therapy with Lopid and Mevacor® (lovastatin) has been associated with rhabdomyolysis, markedly elevated creatine kinase (CK) levels and myoglobinuria, leading in a high proportion of cases to acute renal failure. IN VIRTUALLY ALL PATIENTS WHO HAVE HAD AN UNSATISFACTORY LIPID RESPONSE TO EITHER DRUG ALONE, ANY POTENTIAL LIPID BENEFIT OF COMBINED THERAPY WITH LOVASTATIN AND GEMFIBROZIL DOES NOT OUTWEIGH THE RISKS OF SEVERE MYOPATHY, RHABDOMYOLYSIS, AND ACUTE RENAL FAILURE (see Drug Interactions). The use of fibrates alone, including Lopid, may occasionally be associated with myositis. Patients receiving Lopid and complaining of muscle pain, tenderness, or weakness should have prompt medical evaluation for myositis, including serum creatine kinase level determination. If myositis is suspected or diagnosed, Lopid therapy should be withdrawn.

6. Cataracts – Subcapsular bilateral cataracts occurred in 10%, and unilateral in 6.3% of male rats treated with gemfibrozil at 10 times the human dose.

PRECAUTIONS

1. **Initial Therapy** – Laboratory studies should be done to ascertain that the lipid levels are consistently abnormal. Before instituting Lopid therapy, every attempt should be made to control serum lipids with appropriate diet, exercise, weight loss in obese patients, and control of any medical problems such as diabetes mellitus and hypothyroidism that are contributing to the lipid abnormalities.

2. **Continued Therapy** – Periodic determination of serum lipids should be obtained, and the drug withdrawn if lipid response is inadequate after 3 months of therapy.

3. **Drug Interactions** – (A) **HMG-CoA reductase inhibitors:** Rhabdomyolysis has occurred with combined gemfibrozil and lovastatin therapy. It may be seen as early as 3 weeks after initiation of combined therapy or after several months. In most subjects who have had an unsatisfactory lipid response to either drug alone, the possible benefit of combined therapy with lovastatin (or other HMG-CoA reductase inhibitors) and gemfibrozil does not outweigh the risks of severe myopathy, rhabdomyolysis, and acute renal failure. There is no assurance that periodic monitoring of creatine kinase will prevent the occurrence of severe myopathy and kidney damage.

(B) **Anticoagulants:** CAUTION SHOULD BE EXERCISED WHEN ANTICOAGULANTS ARE GIVEN IN CONJUNCTION WITH LOPID. THE DOSAGE OF THE ANTICOAGULANT SHOULD BE REDUCED TO MAINTAIN THE PROTHROMBIN TIME AT THE DESIRED LEVEL TO PREVENT BLEEDING COMPLICATIONS. FREQUENT PROTHROMBIN DETERMINATIONS ARE ADVISABLE UNTIL IT HAS BEEN DEFINITELY DETERMINED THAT THE PROTHROMBIN LEVEL HAS STABILIZED.

4. **Carcinogenesis, Mutagenesis, Impairment of Fertility** – Long-term studies have been conducted in rats at 0.2 and 2 times the human dose (based on surface area, mg/meter^2). The incidence of benign liver nodules and liver carcinomas was significantly increased in high dose male rats. The incidence of liver carcinomas increased also in low dose males, but this increase was not statistically significant ($p = 0.1$). Male rats had a dose-related and statistically significant increase of benign Leydig cell tumors. The higher dose female rats had a significant increase in the combined incidence of benign, and malignant liver neoplasms.

Long-term studies have been conducted in mice at 0.1 and 1 times the human dose (based on surface area). There were no statistically significant differences from controls in the incidence of liver tumors, but the doses tested were lower than those shown to be carcinogenic with other fibrates.

Electron microscopy studies have demonstrated a florid hepatic peroxisome proliferation following Lopid administration to the male rat. An adequate study to test for peroxisome proliferation has not been done in humans but changes in peroxisome morphology have been observed. Peroxisome proliferation has been shown to occur in humans with either of two other drugs of the fibrate class when liver biopsies were compared before and after treatment in the same individual.

Administration of approximately 0.6 and 2 times the human dose (based on surface area) to male rats for 10 weeks resulted in a dose-related decrease of fertility. Subsequent studies demonstrated that this effect was reversed after a drug-free period of about eight weeks, and it was not transmitted to the offspring.

5. **Pregnancy Category C** – Lopid has been shown to produce adverse effects in rats and rabbits at doses between 0.5 and 3 times the human dose (based on surface area) but no developmental toxicity or teratogenicity among offspring of either species. There are no adequate and well-controlled studies in pregnant women. Lopid should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Administration of Lopid to female rats at 0.6 and 2 times the human dose (based on surface area) before and throughout gestation caused a dose-related decrease in conception rate and, at the high dose, an increase in stillborns and a slight reduction in pup weight during lactation. There were also dose-related increased skeletal variations. Anophthalmia occurred, but rarely.

Administration of 0.6 and 2 times the human dose (based on surface area) of Lopid to female rats from gestation day 15 through weaning caused dose-related decreases in birth weight and suppressions of pup growth during lactation.

Administration of 1 and 3 times the human dose (based on surface area) of Lopid to female rabbits during organogenesis caused a dose-related decrease in litter size and at the high dose, an increased incidence of parietal bone variations.

6. **Nursing Mothers** – It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for tumorigenicity shown for Lopid in animal studies, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

7. **Hematologic Changes** – Mild hemoglobin, hematocrit and white blood cell decreases have been observed in occasional patients following initiation of Lopid therapy. However, these levels stabilize during long-term administration. Rarely, severe anemia, leukopenia, thrombocytopenia, and bone marrow hypoplasia have been reported. Therefore, periodic blood counts are recommended during the first 12 months of Lopid administration.

8. **Liver Function** – Abnormal liver function tests have been observed occasionally during Lopid administration, including elevations of AST (SGOT), ALT (SGPT), LDH, bilirubin, and alkaline phosphatase. These are usually reversible when Lopid is discontinued. Therefore periodic liver function studies are recommended and Lopid therapy should be terminated if abnormalities persist.

9. **Kidney Function** – There have been reports of worsening renal insufficiency upon the addition of Lopid therapy in individuals with baseline plasma creatinine > 2.0 mg/dL. In such patients, the use of alternative therapy should be considered against the risks and benefits of a lower dose of Lopid.

10. **Use in Children** – Safety and efficacy in children and adolescents have not been established.

ADVERSE REACTIONS

In the double-blind controlled phase of the primary prevention component of the Helsinki Heart Study, 2046 patients received Lopid for up to 5 years. In that study, the following adverse reactions were statistically more frequent in subjects in the Lopid group:

	LOPID (N=2046)	PLACEBO (N=2035)
	Frequency in percent of subjects	
Gastrointestinal reactions	34.2	23.8
Dyspepsia	19.6	11.9
Abdominal pain	9.8	5.6
Acute appendicitis (histologically confirmed in most cases where data were available)	1.2	0.6
Atrial fibrillation	0.7	0.1
Adverse events reported by more than 1% of subjects, but without a significant difference between groups:		
Diarrhea	7.2	6.5
Fatigue	3.8	3.5
Nausea/Vomiting	2.5	2.1
Eczema	1.9	1.2
Rash	1.7	1.3
Vertigo	1.5	1.3
Constipation	1.4	1.3
Headache	1.2	1.1

Gallbladder surgery was performed in 0.9% of Lopid and 0.5% of placebo subjects in the primary prevention component, a 64% excess, which is not statistically different from the excess of gallbladder surgery observed in the clofibrate compared to the placebo group of the WHO study. Gallbladder surgery was also performed more frequently in the Lopid group compared to placebo (1.9% vs. 0.3%, $p = 0.07$) in the secondary prevention component. A statistically significant increase in appendectomy in the gemfibrozil group was seen also in the secondary prevention component (6 on gemfibrozil vs. 0 on placebo, $p = 0.014$).

Nervous system and special senses adverse reactions were more common in the Lopid group. These included hypesthesia, paresthesias, and taste perversion. Other adverse reactions that were more common among Lopid treatment group subjects but where a causal relationship was not established include cataracts, peripheral vascular disease, and intracerebral hemorrhage.

From other studies it seems probable that Lopid is causally related to the occurrence of MUSCULOSKELETAL SYMPTOMS (see WARNINGS), and to ABNORMAL LIVER FUNCTION TESTS and HEMATOLOGIC CHANGES (see PRECAUTIONS).

Reports of viral and bacterial infections (common cold, cough, urinary tract infections) were more common in gemfibrozil treated patients in other controlled clinical trials of 805 patients. Additional adverse reactions that have been reported for gemfibrozil are listed below by system. These are categorized according to whether a causal relationship to treatment with Lopid is probable or not established:

CAUSAL RELATIONSHIP PROBABLE: *Gastrointestinal:* cholestatic jaundice; *Central Nervous System:* dizziness, somnolence, paresthesia, peripheral neuritis, decreased libido, depression, headache; *Eye:* blurred vision; *Genitourinary:* impotence; *Musculoskeletal:* myopathy, myasthenia, myalgia, painful extremities, arthralgia, synovitis, rhabdomyolysis (see WARNINGS and Drug Interactions under PRECAUTIONS); *Clinical Laboratory:* increased creatine phosphokinase, increased bilirubin, increased liver transaminases (AST [SGOT], ALT [SGPT]), increased alkaline phosphatase; *Hematopoietic:* anemia, leukopenia, bone marrow hypoplasia, eosinophilia; *Immunologic:* angioedema, laryngeal edema, urticaria; *Integumentary:* exfoliative dermatitis, rash, dermatitis, pruritus.

CAUSAL RELATIONSHIP NOT ESTABLISHED: *General:* weight loss; *Cardiac:* extrasystoles; *Gastrointestinal:* pancreatitis, hepatoma, colitis; *Central Nervous System:* confusion, convulsions, syncope; *Eye:* retinal edema; *Genitourinary:* decreased male fertility, renal dysfunction; *Clinical Laboratory:* positive antinuclear antibody; *Hematopoietic:* thrombocytopenia; *Immunologic:* anaphylaxis, Lupus-like syndrome, vasculitis; *Integumentary:* alopecia.

DOSAGE AND ADMINISTRATION

The recommended dose for adults is 1200 mg administered in two divided doses 30 minutes before the morning and evening meal.

OVERDOSAGE

While there has been no reported case of overdosage, symptomatic supportive measures should be taken should it occur.

HOW SUPPLIED

Lopid (Tablet 737), white, elliptical, film-coated, scored tablets, each containing 600 mg gemfibrozil, are available as follows:

N 0071-0737-20 Bottles of 60
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Storage: Store below 30° C (86° F).

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Revised April 1992

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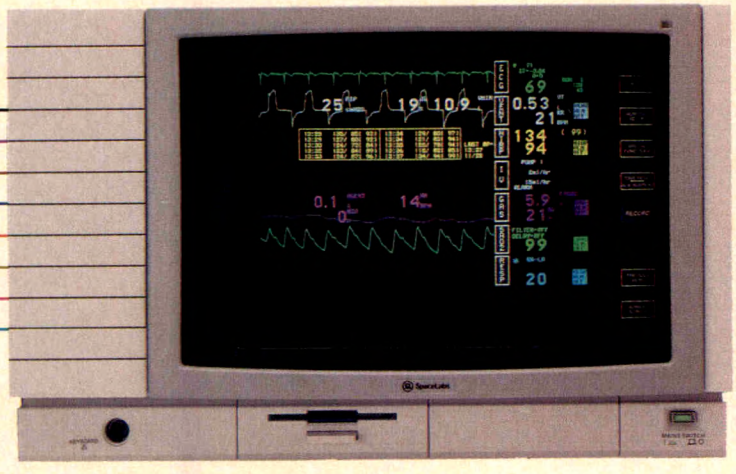
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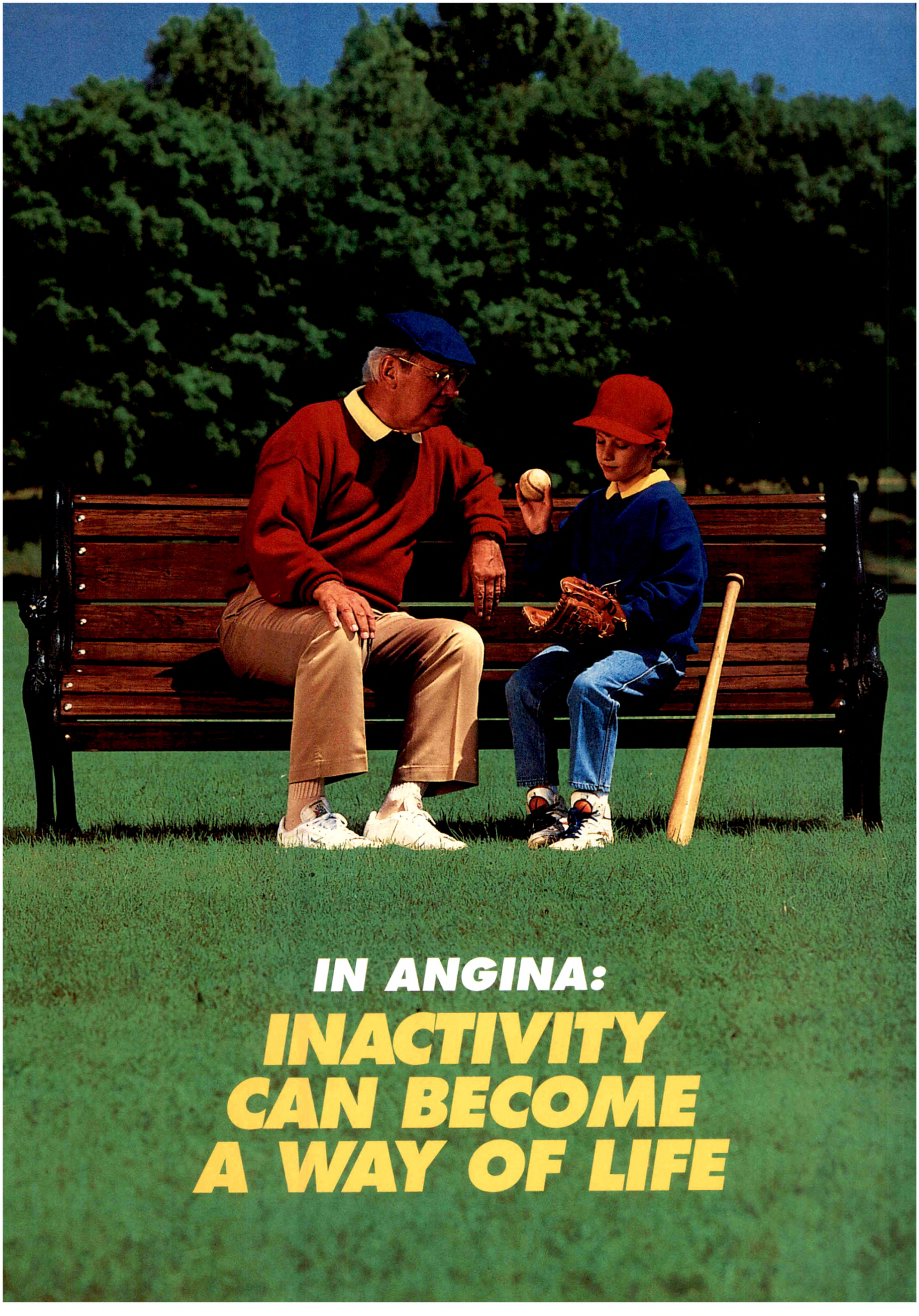
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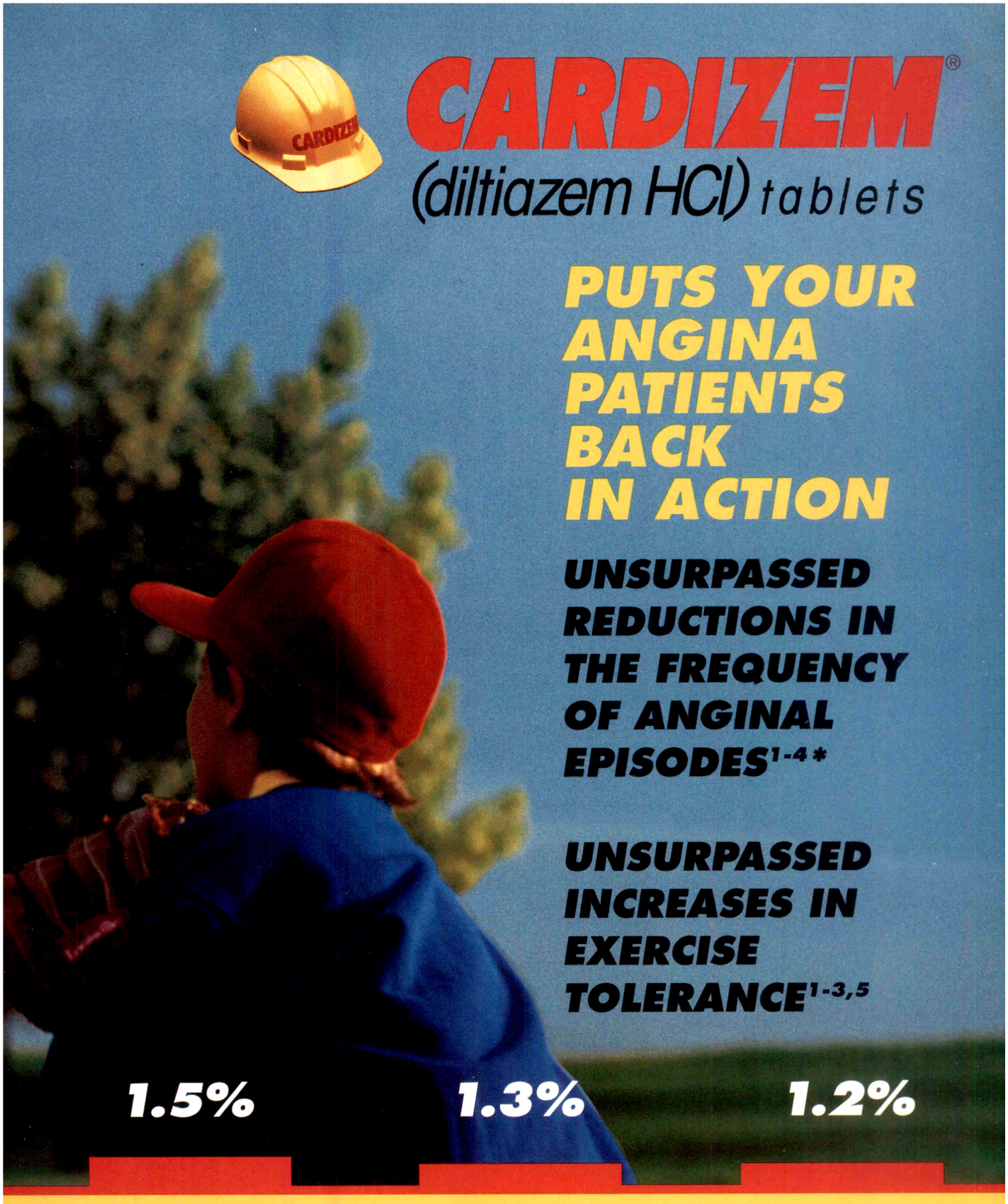


EDEMA **HEADACHE** **NAUSEA**

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* CARDIZEM® (diltiazem HCl) tablets are indicated in the treatment of angina pectoris due to coronary artery spasm and in the management
symptomatic despite adequate doses of these agents.

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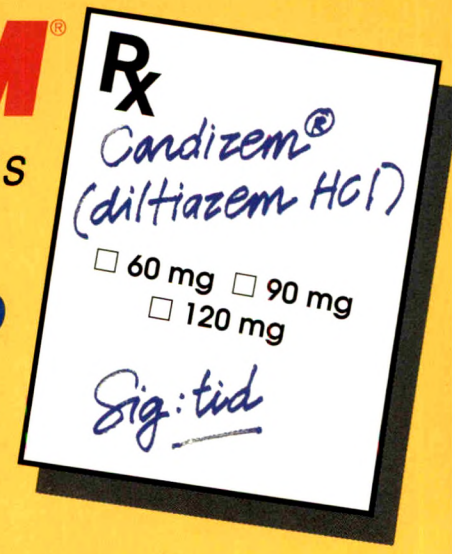
c stable angina (classic effort-associated angina) in patients who cannot tolerate therapy with beta-blockers and/or nitrates or who remain

Please see brief summary of prescribing information on adjacent page.



CARDIZEM®
(diltiazem HCl) tablets

UNSURPASSED EFFICACY AND SAFETY



References:
1. Frishman W, Charlap S, Kimmel B, et al. *Circulation.* 1988;77:774-786. **2.** Klinke WP, Kvill L, Dempsey EE, Grace M. *J Am Coll Cardiol.* 1988;12:1562-1567. **3.** Hung J, Lamb IH, Connolly SJ, Jutzy KR, Goris ML, Schroeder JS. *Circulation.* 1983;68:560-567. **4.** L'Abbate A, Parodi O, Panciroli C, et al. *Cardiology Board Review.* 1989;6 (suppl):50-54. **5.** Anderson JL, Wagner JM, Datz FL, Christian PE, Bray BE, Taylor AT. *Am Heart J.* 1984;107:698-706. **6.** Data on file, Marion Merrell Dow Inc.

BRIEF SUMMARY
CARDIZEM®
(diltiazem hydrochloride) Tablets

CONTRAINDICATIONS

CARDIZEM is contraindicated in (1) patients with sick sinus syndrome except in the presence of a functioning ventricular pacemaker, (2) patients with second- or third-degree AV block except in the presence of a functioning ventricular pacemaker, (3) patients with hypotension (less than 90 mm Hg systolic), (4) patients who have demonstrated hypersensitivity to the drug, and (5) patients with acute myocardial infarction and pulmonary congestion documented by x-ray on admission.

WARNINGS

1. **Cardiac Conduction.** CARDIZEM prolongs AV node refractory periods without significantly prolonging sinus node recovery time, except in patients with sick sinus syndrome. This effect may rarely result in abnormally slow heart rates (particularly in patients with sick sinus syndrome) or second- or third-degree AV block (six of 1,243 patients for 0.48%). Concomitant use of diltiazem with beta-blockers or digitalis may result in additive effects on cardiac conduction. A patient with Prinzmetal's angina developed periods of asystole (2 to 5 seconds) after a single dose of 60 mg of diltiazem.
2. **Congestive Heart Failure.** Although diltiazem has a negative inotropic effect in isolated animal tissue preparations, hemodynamic studies in humans with normal ventricular function have not shown a reduction in cardiac index nor consistent negative effects on contractility (dp/dt). Experience with the use of CARDIZEM alone or in combination with beta-blockers in patients with impaired ventricular function is very limited. Caution should be exercised when using the drug in such patients.
3. **Hypotension.** Decreases in blood pressure associated with CARDIZEM therapy may occasionally result in symptomatic hypotension.
4. **Acute Hepatic Injury.** In rare instances, significant elevations in enzymes such as alkaline phosphatase, LDH, SGOT, SGPT, and other phenomena consistent with acute hepatic injury have been noted. These reactions have been reversible upon discontinuation of drug therapy. The relationship to CARDIZEM is uncertain in most cases, but probable in some. (See PRECAUTIONS.)

PRECAUTIONS

General. CARDIZEM (diltiazem hydrochloride) is extensively metabolized by the liver and excreted by the kidneys and in bile. As with any drug given over prolonged periods, laboratory parameters should be monitored at regular intervals. The drug should be used with caution in patients with impaired renal or hepatic function. In subacute and chronic dog and rat studies designed to produce toxicity, high doses of diltiazem were associated with hepatic damage. In special subacute hepatic studies, oral doses of 125 mg/kg and higher in rats were associated with histological changes in the liver which were reversible when the drug was discontinued. In dogs, doses of 20 mg/kg were also associated with hepatic changes; however, these changes were reversible with continued dosing.

Dermatological events (see ADVERSE REACTIONS section) may be transient and may disappear despite continued use of CARDIZEM. However, skin eruptions progressing to erythema multiforme and/or exfoliative dermatitis have also been infrequently reported. Should a dermatologic reaction persist, the drug should be discontinued.

Drug Interaction. Due to the potential for additive effects, caution and careful titration are warranted in patients receiving CARDIZEM concomitantly with any agents known to affect cardiac contractility and/or conduction. (See WARNINGS.)

Pharmacologic studies indicate that there may be additive effects in prolonging AV conduction when using beta-blockers or digitalis concomitantly with CARDIZEM. (See WARNINGS.)

As with all drugs, care should be exercised when treating patients with multiple medications. CARDIZEM undergoes biotransformation by cytochrome P-450 mixed function oxidase. Coadministration of CARDIZEM with other agents which follow the same route of biotransformation may result in the competitive inhibition of metabolism. Dosages of similarly metabolized drugs, particularly those of low therapeutic ratio or in patients with renal and/or hepatic impairment, may require adjustment when starting or stopping concomitantly administered CARDIZEM to maintain optimum therapeutic blood levels.

Beta-blockers: Controlled and uncontrolled domestic studies suggest that concomitant use of CARDIZEM and beta-blockers or digitalis is usually well tolerated. Available data are not sufficient, however, to predict the effects of concomitant treatment, particularly in patients with left ventricular dysfunction or cardiac conduction abnormalities.

Administration of CARDIZEM (diltiazem hydrochloride) concomitantly with propranolol in five normal volunteers resulted in increased propranolol levels in all subjects and bioavailability of propranolol was increased approximately 50%. If combination therapy is initiated or withdrawn in conjunction with propranolol, an adjustment in the propranolol dose may be warranted. (See WARNINGS.)

Cimetidine: A study in six healthy volunteers has shown a significant increase in peak diltiazem plasma levels (58%) and area-under-the-curve (53%) after a 1-week course of cimetidine at 1,200 mg per day and diltiazem 60 mg per day. Ranitidine produced smaller, nonsignificant increases. The effect may be mediated by cimetidine's known inhibition of hepatic cytochrome P-450, the enzyme system probably responsible for the first-pass metabolism of diltiazem. Patients currently receiving diltiazem therapy should be carefully monitored for a change in pharmacological effect when initiating and discontinuing therapy with cimetidine. An adjustment in the diltiazem dose may be warranted.

Digitalis: Administration of CARDIZEM with digoxin in 24 healthy male subjects increased plasma digoxin concentrations approximately 20%. Another investigator found no increase in digoxin levels in 12 patients with coronary artery disease. Since there have been conflicting results regarding the effect of digoxin levels, it is recommended that digoxin levels be monitored when initiating, adjusting, and discontinuing CARDIZEM therapy to avoid possible over- or under-digitalization. (See WARNINGS.)

Anesthetics: The depression of cardiac contractility, conductivity, and automaticity as well as the vascular dilation associated with anesthetics may be potentiated by calcium channel blockers. When used concomitantly, anesthetics and calcium blockers should be titrated carefully.

Carcinogenesis, Mutagenesis, Impairment of Fertility. A 24-month study in rats and a 21-month study in mice showed no evidence of carcinogenicity. There was also no mutagenic response in in vitro bacterial tests. No intrinsic effect on fertility was observed in rats.

Pregnancy. Category C. Reproduction studies have been conducted in mice, rats, and rabbits. Administration of doses ranging from five to ten times greater (on a mg/kg basis) than the daily recommended therapeutic dose has resulted in embryo and fetal lethality. These doses, in some studies, have been reported to cause skeletal abnormalities. In the perinatal/postnatal studies, there was some reduction in early individual pup weights and survival rates. There was an increased incidence of stillbirths at doses of 20 times the human dose or greater.

There are no well-controlled studies in pregnant women; therefore, use CARDIZEM in pregnant women only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers. Diltiazem is excreted in human milk. One report suggests that concentrations in breast milk may approximate serum levels. If use of CARDIZEM is deemed essential, an alternative method of infant feeding should be instituted.

Pediatric Use. Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Serious adverse reactions have been rare in studies carried out to date, but it should be recognized that patients with impaired ventricular function and cardiac conduction abnormalities have usually been excluded.

In domestic placebo-controlled angina trials, the incidence of adverse reactions reported during CARDIZEM therapy was not greater than that reported during placebo therapy.

The following represent occurrences observed in clinical studies of angina patients. In many cases, the relationship to CARDIZEM has not been established. The most common occurrences from these studies, as well as their frequency of presentation, are: edema (2.4%), headache (2.1%), nausea (1.9%), dizziness (1.5%), rash (1.3%), asthenia (1.2%). In addition, the following events were reported infrequently (less than 1%):

Cardiovascular:	Angina, arrhythmia, AV block (first degree), AV block (second or third degree—see conduction warning), bradycardia, bundle branch block, congestive heart failure, ECG abnormality, flushing, hypotension, palpitations, syncope, tachycardia, ventricular extrasystoles.
Nervous System:	Abnormal dreams, amnesia, depression, gait abnormality, hallucinations, insomnia, nervousness, paresthesia, personality change, somnolence, tremor.
Gastrointestinal:	Anorexia, constipation, diarrhea, dysgeusia, dyspepsia, mild elevations of alkaline phosphatase, SGOT, SGPT, and LDH (see hepatic warnings), thirst, vomiting, weight increase.
Dermatological:	Petechiae, photosensitivity, pruritus, urticaria.
Other:	Amblyopia, CPK elevation, dry mouth, dyspnea, epistaxis, eye irritation, hyperglycemia, hyperuricemia, impotence, muscle cramps, nasal congestion, nocturia, osteoarticular pain, polyuria, sexual difficulties, tinnitus.

The following postmarketing events have been reported infrequently in patients receiving CARDIZEM: alopecia, erythema multiforme, extrapyramidal symptoms, gingival hyperplasia, hemolytic anemia, increased bleeding time, leukopenia, purpura, retinopathy, and thrombocytopenia. There have been observed cases of a generalized rash, characterized as leukocytoclastic vasculitis. In addition, events such as myocardial infarction have been observed which are not readily distinguishable from the natural history of the disease in these patients. A definitive cause and effect relationship between these events and CARDIZEM therapy cannot yet be established. Exfoliative dermatitis (proven by rechallenge) has also been reported.

HOW SUPPLIED

CARDIZEM® (diltiazem hydrochloride) is available in bottles of 90 (60 mg, 90 mg, 120 mg tablets), bottles of 100 (30 mg, 60 mg, 90 mg, 120 mg tablets), bottles of 500 (30 mg, 60 mg tablets), and UDIP® packages of 100.

Issued 1/91(a)

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KANSAS CITY, MO 64114

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SEPTEMBER 1, 1992, VOL. 70, NO. 6

CORONARY ARTERY DISEASE

567

Performance Status and Outcome After Coronary Artery Bypass Grafting in Persons Aged 80 to 93 Years

Donald D. Glower, Thomas D. Christopher, Carmelo A. Milano, William D. White, L. Richard Smith, Robert H. Jones, and David C. Sabiston, Jr.

Preoperative, intraoperative and postoperative characteristics and pre- and postoperative performance status (Karnofsky score) were examined in 86 consecutive patients aged 80 to 93 years undergoing isolated coronary artery bypass grafting. The rate of significant in-hospital complications was 29%, and median performance status improved from 20 to 70%, with 88% of hospital survivors being discharged home. Factors associated with failure to achieve a successful functional outcome at discharge were presence of 1 or more preoperative co-morbid conditions, preoperative myocardial infarction within 7 days of operation, and postoperative low cardiac output. Survival at 30 days and 3 years was 90 and 64%, respectively. These data suggest that coronary artery bypass can be offered to elderly patients with acceptable morbidity and mortality, marked improvement in performance status, and an acceptable quality of life.

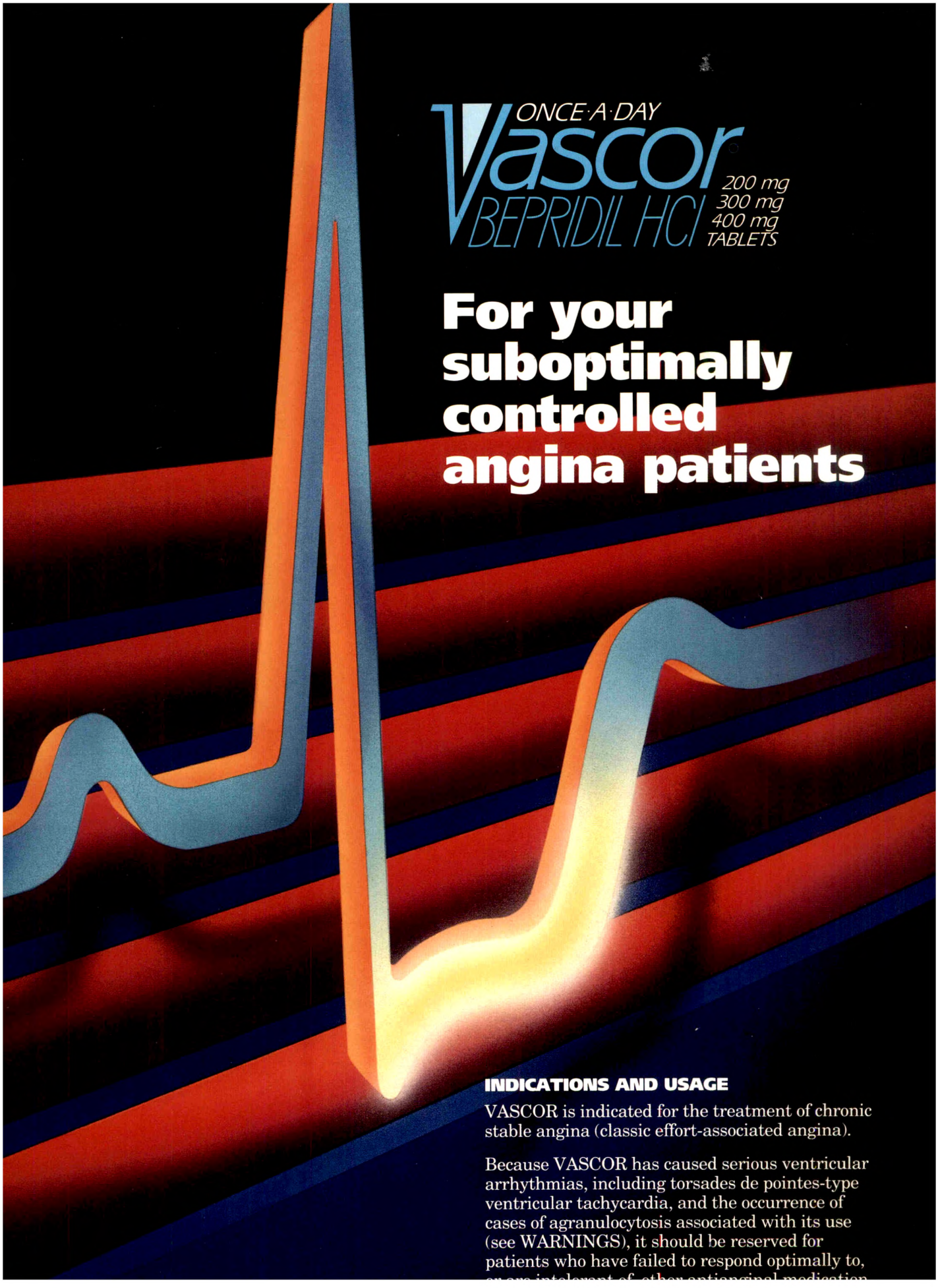
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Exercise Echocardiography After Coronary Artery Bypass Grafting

Linda J. Crouse, James L. Vacek, Gary D. Beauchamp, Charles B. Porter, Thomas L. Rosamond, and Paul H. Kramer

Patients who have undergone coronary artery bypass grafting (CABG) are at risk for graft failure and progressive disease in ungrafted vessels. Symptomatic and traditional exercise electrocardiographic follow-up of these patients has proven to be less than satisfactory for the outpatient follow-up of CABG patients. This report describes the applicability of treadmill exercise echocardiography in depicting the presence or absence of regional coronary insufficiency in CABG patients. The results of stress echocardiography are compared with those of stress electrocardiography and (in all patients) angiography. Using the angiogram as the gold standard, stress echocardiography was more sensitive (98 vs 41%) and specific (92 vs 67%), and had higher positive and negative predictive values (99 vs 91% and 86 vs 12%, respectively). In addition, exercise echocardiography correlated closely with the extent and regional distribution of compromised vascular supply. Thus, exercise echocardiography appears to be an excellent tool for the outpatient monitoring of CABG patients.

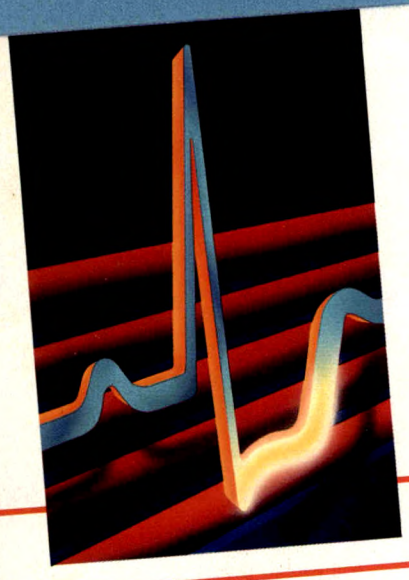
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INDICATIONS AND USAGE

VASCOR is indicated for the treatment of chronic stable angina (classic effort-associated angina).

Because VASCOR has caused serious ventricular arrhythmias, including torsades de pointes-type ventricular tachycardia, and the occurrence of cases of agranulocytosis associated with its use (see WARNINGS), it should be reserved for patients who have failed to respond optimally to, or are intolerant of, other antianginal medication



Another in a series of actual case reports

A CASE FOR VASCOR® (bepridil HCl)

James P., 58-year-old building painter*

PRESENTING SYMPTOM: Could not continue to work because of limiting angina

HISTORY: Suboptimal response to a regimen of atenolol, diltiazem, and isosorbide dinitrate; remains uncontrolled despite angioplasty

EXERCISE TOLERANCE TEST:
Total exercise time: 5 min, 1 sec
Time to 1-mm ST depression: 3 min, 12 sec
Time to onset of angina: 2 min, 52 sec

LABORATORY FINDINGS:
Serum potassium: 4.3 mEq/L
ECG: Nonspecific ST abnormality
QTc interval: 406 msec

CLINICAL COURSE: Diltiazem discontinued; VASCOR 200 mg QD initiated, resulting in some improvement after 2 weeks; VASCOR dosage increased to 300 mg QD, resulting in marked improvement after 4 weeks

EXERCISE TOLERANCE TEST:
Total exercise time: 6 min, 1 sec
Time to 1-mm ST depression: 4 min, 12 sec
Time to onset of angina: 4 min, 2 sec
QTc interval range: 440 to 460 msec

FOLLOW-UP: **Over the next 3 months, James P. was able to return to his job part-time and experienced angina only with extreme exertion**

ONCE·A·DAY Vascor® BEPRIDIL HCl 200 mg 300 mg 400 mg TABLETS

*Based on an actual case history submitted by Stephen P. Glasser, MD, Director of the Cardiovascular Unit for Research and Education, University of South Florida Health Science Center.

Please see brief summary of prescribing information.

McNEIL PHARMACEUTICAL

WALLACE LABORATORIES

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V793C 3/92

VASCOR® (bepridil hydrochloride)

Tablets For Oral Administration

Brief Summary

INDICATIONS AND USAGE

Chronic Stable Angina (Classic Effort-Associated Angina)

VASCOR (bepridil hydrochloride) is indicated for the treatment of chronic stable angina (classic effort-associated angina). Because VASCOR has caused serious ventricular arrhythmias, including torsades de pointes type ventricular tachycardia, and the occurrence of cases of agranulocytosis associated with its use (see WARNINGS), it should be reserved for patients who have failed to respond optimally to, or are intolerant of, other anti-anginal medication.

VASCOR may be used alone or in combination with beta blockers and/or nitrates. Controlled clinical studies have shown an added effect when VASCOR is administered to patients already receiving propranolol.

CONTRAINDICATIONS

VASCOR (bepridil hydrochloride) is contraindicated in patients with a known sensitivity to bepridil hydrochloride.

VASCOR is contraindicated in (1) patients with a history of serious ventricular arrhythmias (see WARNINGS–Induction of New Serious Arrhythmias), (2) patients with sick sinus syndrome or patients with second- or third-degree AV block, except in the presence of a functioning ventricular pacemaker, (3) patients with hypotension (less than 90 mm Hg systolic), (4) patients with uncompensated cardiac insufficiency, (5) patients with congenital QT interval prolongation (see WARNINGS), and (6) patients taking other drugs that prolong QT interval (see PRECAUTIONS-Drug Interactions).

WARNINGS

Induction of New Serious Arrhythmias

VASCOR (bepridil hydrochloride) has Class 1 anti-arrhythmic properties and, like other such drugs, can induce new arrhythmias, including VT/VF. In addition, because of its ability to prolong the QT interval, VASCOR can cause torsades de pointes type ventricular tachycardia. Because of these properties VASCOR should be reserved for patients in whom other anti-anginal agents do not offer a satisfactory effect.

In US clinical trials, the QT and QTc intervals were commonly prolonged by VASCOR in a dose-related fashion. While the mean prolongation of QTc was 8% and of QT was 10%, QTc increases of 25% or more were not uncommon, 5%; 8.7% QT. Increased QT and QTc may be associated with torsades de pointes type VT, which was seen at least briefly, in about 1.0% of patients in US trials; in many cases, however, patients with marked prolongation of QTc were taken off VASCOR therapy. All of the US patients with torsades de pointes had a prolonged QT interval and relatively low serum potassium. French marketing experience has reported over one hundred verified cases of torsades de pointes. While this number, based on total use, represents a rate of only 0.01%, the true rate is undoubtedly much higher, as spontaneous reporting systems all suffer from substantial under reporting.

Torsades de pointes is a polymorphic ventricular tachycardia often but not always associated with a prolonged QT interval, and often drug induced. The relation between the degree of QT prolongation and the development of torsades de pointes is not linear and the likelihood of torsades appears to be increased by hypokalemia, use of potassium wasting diuretics, and the presence of antecedent bradycardia. While the safe upper limit of QT is not defined, it is suggested that the interval not be permitted to exceed 0.52 seconds during treatment. If dose reduction does not eliminate the excessive prolongation, VASCOR should be stopped.

Because most domestic and foreign cases of torsades have developed in patients with hypokalemia, usually related to diuretic use or significant liver disease, if concomitant diuretics are needed, low doses and addition or primary use of a potassium sparing diuretic should be considered and serum potassium should be monitored.

VASCOR has been associated with the usual range of pro-arrhythmic effects characteristic of Class 1 anti-arrhythmics (increased premature ventricular contraction rates, new sustained VT, and VT/VF that is more difficult than previously to convert to sinus rhythm). Use in patients with severe arrhythmias (who are most susceptible to certain pro-arrhythmic effects) has been limited, so that risk in these patients is not defined.

In the National Heart, Lung and Blood Institute's Cardiac Arrhythmia Suppression Trial (CAST), a long-term, multi-centered, randomized, double-blind study in patients with asymptomatic nonlife-threatening ventricular arrhythmias who had myocardial infarctions more than six days but less than two years previously, an excess mortality/non-fatal cardiac arrest rate was seen in patients treated with encainide or flecainide (56/730) compared with that seen in patients assigned to matched placebo-treated groups (22/725). The applicability of these results to other populations (e.g., those without recent myocardial infarction) or to other anti-arrhythmic drugs is uncertain, but at present it is prudent to consider any drug documented to provoke new serious arrhythmias or worsening of preexisting arrhythmias as having a similar risk and to avoid their use in the post-infarction period.

Agranulocytosis: In US clinical trials of over 800 patients treated with VASCOR for up to five years, two cases of marked leukopenia and neutropenia were reported. Both patients were diabetic and elderly. One died with overwhelming gram-negative sepsis, itself a possible cause of marked leukopenia. The other patient recovered rapidly when VASCOR was stopped.

Congestive Heart Failure: Congestive heart failure has been observed infrequently (about 1%) during US controlled clinical trials, but experience with the use of VASCOR in patients with significantly impaired ventricular function is limited. There is little information on the effect of concomitant administration of VASCOR and digoxin; therefore, caution should be exercised in treating patients with congestive heart failure.

Hepatic Enzyme Elevation: In US clinical studies with VASCOR in about 1000 patients and subjects, clinically significant (at least 2 times the upper limit of normal) transaminase elevations were observed in approximately 1% of the patients. None of these patients became clinically symptomatic or jaundiced and values returned to normal when the drug was stopped.

Hypokalemia: In clinical trials VASCOR has not been reported to reduce serum potassium levels. Because hypokalemia has been associated with ventricular arrhythmias, potassium insufficiency should be corrected before VASCOR therapy is initiated and normal potassium concentrations should be maintained during VASCOR therapy. Serum potassium should be monitored periodically.

PRECAUTIONS

General

Caution should be exercised when using VASCOR (bepridil hydrochloride) in patients with left bundle branch block or sinus bradycardia (less than 50 b.p.m.). Care should also be exercised in patients with serious hepatic or renal disorders because such patients have not been studied and bepridil is highly metabolized, with metabolites excreted primarily in the urine.

Recent Myocardial Infarction

In US clinical trials with VASCOR, patients with myocardial infarctions within three months prior to initiation of drug treatment were excluded. The initiation of VASCOR therapy in such patients, therefore, cannot be recommended.

Information for Patients

Since QT prolongation is not associated with defined symptomatology, patients should be instructed on the importance of maintaining any potassium supplementation or potassium sparing diuretic, and the need for routine electrocardiograms and periodic monitoring of serum potassium.

The following Patient Information is printed on the carton label of each unit of use bottle of 30 tablets:

As with any medication that you take, you should notify your physician of any changes in your overall condition. Insure that you follow your physician's instructions regarding follow-up visits. Please notify any physician who treats you for a medical condition that you are taking VASCOR® (bepridil hydrochloride), as well as any other medications.

Drug Interactions

Nitrates: The concomitant use of VASCOR with long- and short-acting nitrates has been safely tolerated in patients with stable angina pectoris. Sublingual nitroglycerin may be taken if necessary for the control of acute angina attacks during VASCOR therapy.

Beta-blocking Agents: The concomitant use of VASCOR and beta-blocking agents has been well tolerated in patients with stable angina. Available data are not sufficient, however, to predict the effects of concomitant medication on patients with impaired ventricular function or cardiac conduction abnormalities (see DOSAGE AND ADMINISTRATION).

Digoxin: In controlled studies in healthy volunteers, bepridil hydrochloride either had no effect (one study) or was associated with modest increases, about 30% (two studies) in steady-state serum digoxin concentrations. Limited clinical data in angina patients receiving concomitant bepridil hydrochloride and digoxin therapy indicate no discernible changes in serum digoxin levels. Available data are neither sufficient to rule out possible increases in serum digoxin with concomitant treatment in some patients, nor other possible interactions, particularly in patients with cardiac conduction abnormalities (also see WARNINGS–Congestive Heart Failure).

Oral Hypoglycemics: VASCOR has been safely used in diabetic patients without significantly lowering their blood glucose levels or altering their need for insulin or oral hypoglycemic agents.

General Interactions: Certain drugs could increase the likelihood of potentially serious adverse effects with bepridil hydrochloride. In general, these are drugs that have one or more pharmacologic activities similar to bepridil hydrochloride, including anti-arrhythmic agents such as quinidine and procainamide, cardiac glycosides and tricyclic anti-depressants. Anti-arrhythmics and tricyclic anti-depressants could exaggerate the prolongation of the QT interval observed with bepridil hydrochloride. Cardiac glycosides could exaggerate the depression of AV nodal conduction observed with bepridil hydrochloride.

Carcinogenesis, Mutagenesis, Impairment of Fertility

No evidence of carcinogenicity was revealed in one lifetime study in mice at dosages up to 60 times (for a 60 kg subject) the maximum recommended dosage in man. Unilateral follicular adenomas of the thyroid were observed in a study in rats following lifetime administration of high doses of bepridil hydrochloride, i.e., ≥ 100 mg/kg/day (20 times the usual recommended dose in man). No mutagenic or other genotoxic potential of bepridil hydrochloride was found in the following standard laboratory tests: the Micronucleus Test for Chromosomal Effects, the Liver Microsome Activated Bacterial Assay for Mutagenicity, the Chinese Hamster Ovary Cell Assay for Mutagenicity, and the Sister Chromatid Exchange Assay. No intrinsic effect on fertility by bepridil hydrochloride was demonstrated in rats.

In monkeys, at 200 mg/kg/day, there was a decrease in testicular weight and spermatogenesis. There were no systematic studies in man related to this point. In rats, at doses up to 300 mg/kg/day, there was no observed alteration of mating behavior nor of reproductive performance.

Usage in Pregnancy

Pregnancy Category C. Reproductive studies (fertility and peri-postnatal) have been conducted in rats. Reduced litter size at birth and decreased pup survival during lactation were observed at maternal dosages 37 times (on a mg/kg basis) the maximum daily recommended therapeutic dosage.

In teratology studies, no effects were observed in rats or rabbits at these same dosages.

There are no well-controlled studies in pregnant women. Use VASCOR in pregnant or nursing women only if the potential benefit justifies the potential risk.

Nursing Mothers

Bepridil is excreted in human milk. Bepridil concentration in human milk is estimated to reach about one third the concentration in serum. Because of the potential for serious adverse reactions in nursing infants from VASCOR a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

The safety and effectiveness of VASCOR in children have not been established.

ADVERSE REACTIONS

Adverse reactions were assessed in 529 patients who received VASCOR (bepridil hydrochloride) in controlled trials of 4-12 weeks duration and longer-term uncontrolled studies. The most common side effects occurring more frequently than in control groups were upper gastrointestinal complaints (nausea, dyspepsia or GI distress) in about 22%, diarrhea in about 8%, dizziness in about 15%, asthenia in about 10% and nervousness in about 7%. The adverse reactions seen in at least 2% of bepridil patients in controlled trials are shown in the following list.

Body as a Whole: Asthenia, Headache, Flu Syndrome **Cardiovascular/Respiratory:** Palpitations, Dyspnea, Respiratory Infection **Gastrointestinal:** Dyspepsia, G.I. Distress, Nausea, Dry Mouth, Anorexia, Diarrhea, Abdominal Pain, Constipation **Central Nervous System:** Drowsy, Insomnia, Dizziness, Tremor, Tremor of Hand, Paresthesia **Psychiatric:** Nervous **Special Senses:** Tinnitus.

About 15% of patients however, left bepridil treatment because of adverse experiences. In controlled clinical trials, these were principally gastrointestinal (1.0%), dizziness (1.0%), ventricular arrhythmias (1.0%) and syncope (0.6%).

Across all controlled and uncontrolled trials, VASCOR was evaluated in over 800 patients with chronic angina. In addition to the adverse reactions noted above, the following were observed in 0.5 to 2.0% of the VASCOR patients or are rarer, but potentially important events seen in clinical studies or reported in post marketing experience. In most cases it is not possible to determine whether there is a causal relationship to bepridil treatment.

Body as a Whole: Fever, pain, myalgic asthenia, superinfection, flu syndrome. **Cardiovascular/Respiratory:** Sinus tachycardia, sinus bradycardia, hypertension, vasodilation, edema, ventricular premature contractions, ventricular tachycardia, prolonged QT interval, rhinitis, cough, pharyngitis. **Gastrointestinal:** Flatulence, gastritis, appetite increase, dry mouth, constipation. **Musculoskeletal:** Arthritis. **Central Nervous System:** Fainting, vertigo, akathisia, drowsiness, insomnia, tremor. **Psychiatric:** Depression, anxiousness, adverse behavior effect. **Skin:** Rash, sweating, skin irritation. **Special Senses:** Blurred vision, tinnitus, taste change. **Urogenital:** Loss of libido, impotence. **Abnormal Lab Values:** Abnormal liver function test, SGPT increase.

Certain cardiovascular events, such as acute myocardial infarction (about 3% of patients) worsened heart failure (1.9%), worsened angina (4.5%), severe arrhythmia (about 2.4% VT/VF) and sudden death (1.6%) have occurred in patients receiving bepridil, but have not been included as adverse events because they appear to be, and cannot be distinguished from, manifestations of the patient's underlying cardiac disease. Such events as torsades de pointes arrhythmias, prolonged QT/QTc, bradycardia, first degree heart block, which are probably related to bepridil, are included in the tables.

OVERDOSAGE

In the event of overdosage, we recommend close observation in a cardiac care facility for a minimum of 48 hours and use of appropriate supportive measures in addition to gastric lavage. Beta-adrenergic stimulation or parenteral administration of calcium solutions may increase transmembrane calcium ion influx. Clinically significant hypotensive reactions or high-degree AV block should be treated with vasopressor agents or cardiac pacing, respectively. Ventricular tachycardia should be handled by cardioversion and, if persistent, by overdrive pacing. There has been one experience with overdosage in which a patient inadvertently took a single dose of 1600 mg of VASCOR (bepridil hydrochloride). The patient was observed for 72 hours in intensive care, but no significant adverse experiences were noted.

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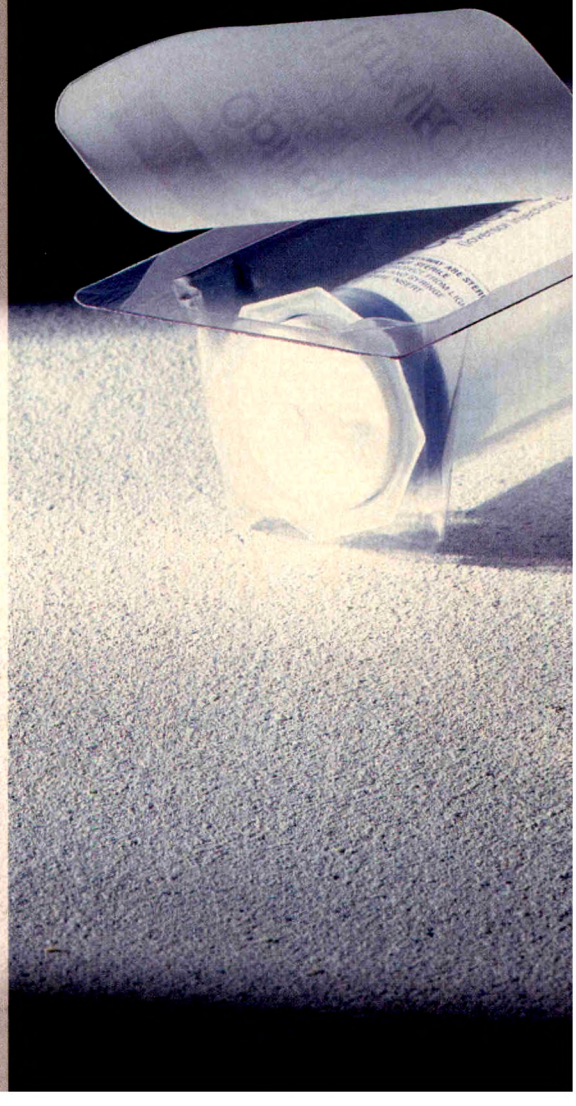
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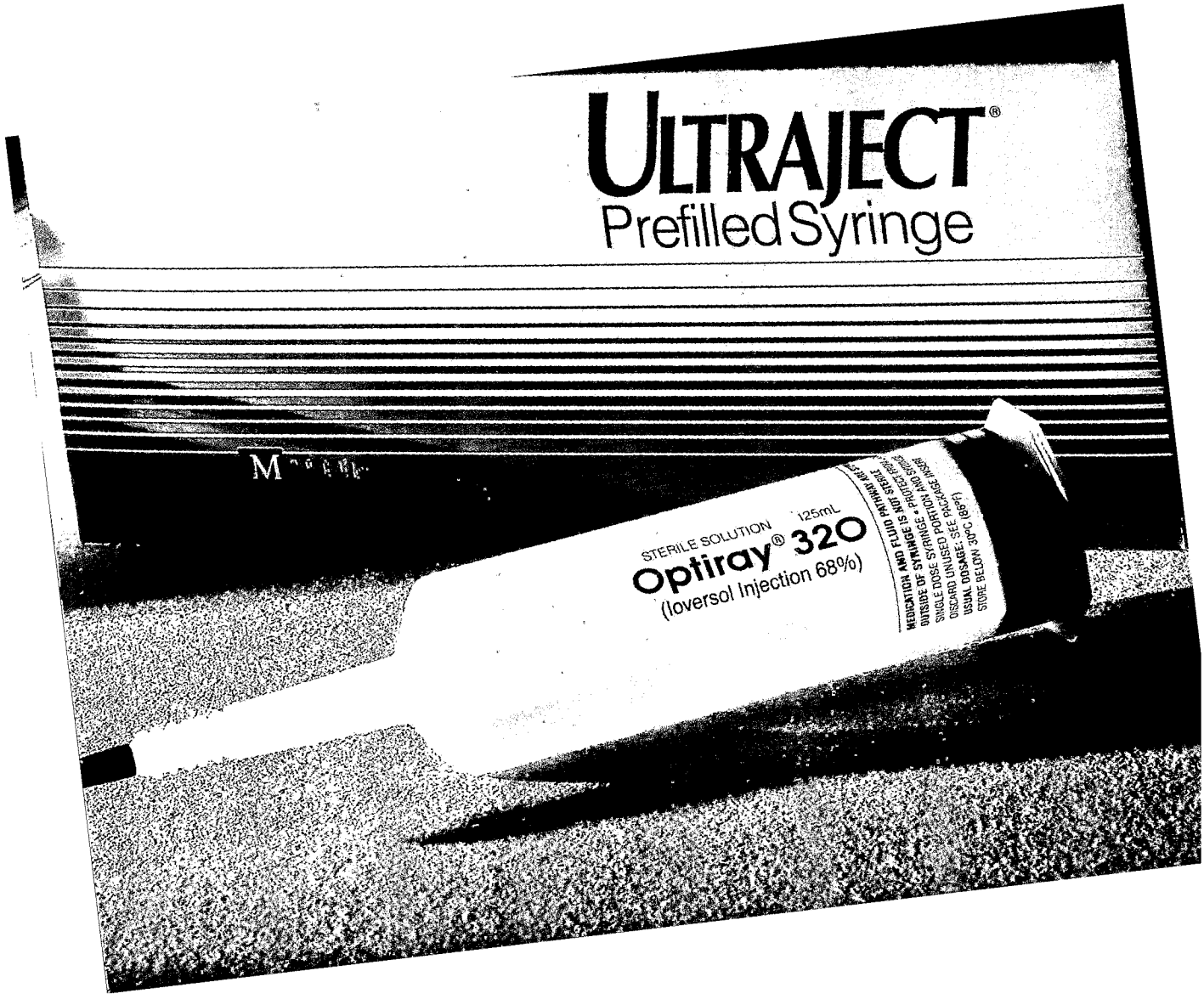
*Hamilton G. Contamination of contrast agents by rubber components of 50-ml disposable syringes. *Radiology*. 1984;152:539-540.

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Effect of Maximal Medical Therapy on Refractoriness of Unstable Angina Pectoris
David W. Grambow and Eric J. Topol

A group of 125 patients with unstable angina were studied over a 5-year period to define the incidence of refractory unstable angina in the current era of 5-drug medical therapy with intravenous heparin, aspirin, nitrates, calcium antagonists and β blockers. At the time of transfer to the center, 65 patients continued to have ischemic chest pain at rest and were considered "medically refractory" by their referring physicians. A more aggressive medical regimen was used, and 54 patients (83%) were rendered chest pain–free. Of the 11 truly refractory patients (8.8%), coronary arteriography revealed an increased likelihood of left main or 3-vessel disease (7 of 11 vs 26 of 114; $p = 0.01$). Refractory patients tended to have more prior coronary artery bypass grafting ($p = 0.07$) and a higher in-hospital rate of myocardial infarction or death ($p = 0.009$). In the current era of polypharmacologic intervention, refractory unstable angina to maximal medical therapy is infrequent (8.8%), with many patients considered refractory becoming chest pain–free with more aggressive medical therapy.

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Normalization of Impaired Response of Platelets to Prostaglandin E_1/I_2 and Synthesis of Prostacyclin by Insulin in Unstable Angina Pectoris and in Acute Myocardial Infarction
Nighat N. Kahn, Mohammad A. Najeeb, Mohammad Ishaq, Abdul Rahim, and Asru K. Sinha

Platelets from patients with unstable angina pectoris or acute myocardial infarction are known to be resistant to the inhibitory effect of prostacyclin (PGI_2). With use of prostaglandin E_1 as a probe for PGI_2, the minimal inhibitory concentration of the prostanoid for complete inhibition of platelet aggregation induced by adenosine diphosphate in platelet-rich plasma from patients ($n = 46$) and normal control subjects ($n = 40$) was found to be 64 ± 30 and 36 ± 16 nM, respectively. Bolus injection of insulin (0.1 U/kg) to 20 of these patients 4 times a day resulted in a decrease in minimal inhibitory concentration of prostaglandin E_1 to 26 ± 12 nM within 24 hours of insulin administration. This decrease could be maintained for ≥ 7 days by repeated administration of the hormone. Hormone treatment also increased plasma PGI_2 levels from 9 ± 2 to 28 ± 10 pM in these patients. In contrast, platelets in 20 patients who received only saline solution had no changes in sensitivity to PGE_1 or in plasma PGI_2 levels during the same period of time.

Continued on page A22

WHY CONSIDER TENORMIN BEFORE ALL OTHER BETA BLOCKERS?



- **Convenient, once-daily dosing for all indications**
- **Effective control of blood pressure and angina**
- **Cardioprotection—improving survival during and after MI[1,2]***
- **Well-tolerated**

I.V. INJECTION/TABLETS

TENORMIN®

(atenolol)

* Good clinical judgment suggests that patients who are dependent on sympathetic stimulation for adequate cardiac output and BP are not good candidates for beta blockade. In addition to patients excluded from the ISIS-1 study, those with borderline BP (ie, systolic < 120, especially if over age 60) are less likely to benefit.

References: 1. ISIS-1 (First International Study of Infarct Survival) Collaborative Group. Randomised trial of intravenous atenolol among 16 027 cases of suspected acute myocardial infarction: ISIS-1. *Lancet.* 1986;2:57-66. **2.** Glamann DB, Lange RA, Hillis LD. Beneficial effect of long-term beta blockade after acute myocardial infarction in patients without anterograde flow in the infarct artery. *Am J Cardiol.* 1991;68:150-154.

See adjacent page for brief summary of prescribing information.

I.V. INJECTION/TABLETS

TENORMIN® (atenolol) 25, 50, 100 mg tablets

(FOR FULL PRESCRIBING INFORMATION, SEE PACKAGE INSERT.)

INDICATIONS AND USAGE: Hypertension: TENORMIN is indicated in the management of hypertension. It may be used alone or concomitantly with other antihypertensive agents, particularly with a thiazide-type diuretic.

Angina Pectoris Due to Coronary Atherosclerosis: TENORMIN is indicated for the long-term management of patients with angina pectoris.

Acute Myocardial Infarction: TENORMIN is indicated in the management of hemodynamically stable patients with definite or suspected acute myocardial infarction to reduce cardiovascular mortality. Treatment can be initiated as soon as the patient's clinical condition allows. (See DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS.) In general, there is no basis for treating patients like those who were excluded from the ISIS-1 trial (blood pressure less than 100 mm Hg systolic, heart rate less than 50 bpm) or have other reasons to avoid beta blockade. As noted above, some subgroups (eg, elderly patients with systolic blood pressure below 120 mm Hg) seemed less likely to benefit.

CONTRAINDICATIONS: TENORMIN is contraindicated in sinus bradycardia, heart block greater than first degree, cardiogenic shock, and overt cardiac failure. (See WARNINGS.)

WARNINGS: Cardiac Failure: Sympathetic stimulation is necessary in supporting circulatory function in congestive heart failure, and beta blockade carries the potential hazard of further depressing myocardial contractility and precipitating more severe failure. In patients who have congestive heart failure controlled by digitalis and/or diuretics, TENORMIN should be administered cautiously. Both digitalis and atenolol slow AV conduction.

In patients with acute myocardial infarction, cardiac failure which is not promptly and effectively controlled by 80 mg of intravenous furosemide or equivalent therapy is a contraindication to beta-blocker treatment.

In Patients Without a History of Cardiac Failure: Continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or be given a diuretic and the response observed closely. If cardiac failure continues despite adequate digitalization and diuresis, TENORMIN should be withdrawn. (See DOSAGE AND ADMINISTRATION.)

Cessation of Therapy with TENORMIN: Patients with coronary artery disease, who are being treated with TENORMIN, should be advised against abrupt discontinuation of therapy. Severe exacerbation of angina and the occurrence of myocardial infarction and ventricular arrhythmias have been reported in angina patients following the abrupt discontinuation of therapy with beta blockers. The last two complications may occur with or without preceding exacerbation of the angina pectoris. As with other beta blockers, when discontinuation of TENORMIN is planned, the patients should be carefully observed and advised to limit physical activity to a minimum. If the angina worsens or acute coronary insufficiency develops, it is recommended that TENORMIN be promptly reinstituted, at least temporarily. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue TENORMIN therapy abruptly even in patients treated only for hypertension. (See DOSAGE AND ADMINISTRATION.)

Bronchospastic Diseases: PATIENTS WITH BRONCHOSPASTIC DISEASE SHOULD, IN GENERAL, NOT RECEIVE BETA BLOCKERS. Because of its relative beta, selectivity, however, TENORMIN may be used with caution in patients with bronchospastic disease who do not respond to, or cannot tolerate, other antihypertensive treatment. Since beta, selectivity is not absolute, the lowest possible dose of TENORMIN should be used with therapy initiated at 50 mg and a beta$_2$-stimulating agent (bronchodilator) should be made available. If dosage must be increased, dividing the dose should be considered in order to achieve lower peak blood levels.

Anesthesia and Major Surgery: It is not advisable to withdraw beta-adrenoreceptor blocking drugs prior to surgery in the majority of patients. However, care should be taken when using anesthetic agents such as those which may depress the myocardium. Vagal dominance, if it occurs, may be corrected with atropine (1-2 mg IV).

Additionally, caution should be used when TENORMIN I.V. Injection is administered concomitantly with such agents.

TENORMIN, like other beta blockers, is a competitive inhibitor of beta-receptor agonists and its effects on the heart can be reversed by administration of such agents: eg, dobutamine or isoproterenol with caution (see section on OVERDOSAGE).

Diabetes and Hypoglycemia: TENORMIN should be used with caution in diabetic patients if a beta-blocking agent is required. Beta blockers may mask tachycardia occurring with hypoglycemia, but other manifestations such as dizziness and sweating may not be significantly affected. At recommended doses TENORMIN does not potentiate insulin-induced hypoglycemia and, unlike nonselective beta blockers, does not delay recovery of blood glucose to normal levels.

Thyrotoxicosis: Beta-adrenergic blockade may mask certain clinical signs (eg, tachycardia) of hyperthyroidism. Patients suspected of having thyroid disease should be monitored closely when administering TENORMIN I.V. Injection. Abrupt withdrawal of beta blockade might precipitate a thyroid storm; therefore, patients suspected of developing thyrotoxicosis from whom TENORMIN therapy is to be withdrawn should be monitored closely. (See DOSAGE AND ADMINISTRATION.)

PRECAUTIONS: General: Patients already on a beta blocker must be evaluated carefully before TENORMIN is administered. Initial and subsequent TENORMIN dosages can be adjusted downward depending on clinical observations including pulse and blood pressure. TENORMIN may aggravate peripheral arterial circulatory disorders.

Impaired Renal Function: The drug should be used with caution in patients with impaired renal function. (SEE DOSAGE AND ADMINISTRATION.)

Drug Interactions: Catecholamine-depleting drugs (eg, reserpine) may have an additive effect when given with beta-blocking agents. Patients treated with TENORMIN plus a catecholamine depletor should therefore be closely observed for evidence of hypotension and/or marked bradycardia which may produce vertigo, syncope, or postural hypotension.

Beta blockers may exacerbate the rebound hypertension which can follow the withdrawal of clonidine. If the two drugs are coadministered, the beta blocker should be withdrawn several days before the gradual withdrawal of clonidine. If replacing clonidine by beta-blocker therapy, the introduction of beta blockers should be delayed for several days after clonidine administration has stopped.

Caution should be exercised with TENORMIN I.V. Injection when given in close proximity with drugs that may also have a depressant effect on myocardial contractility. On rare occasions, concomitant use of intravenous beta blockers and intravenous verapamil has resulted in serious adverse reactions, especially in patients with severe cardiomyopathy, congestive heart failure, or recent myocardial infarction.

Information on concurrent usage of atenolol and aspirin is limited. Data from several studies, ie, TIMI-II, ISIS-2, currently do not suggest any clinical interaction between aspirin and beta blockers in the acute myocardial infarction setting.

While taking beta blockers, patients with a history of anaphylactic reaction to a variety of allergens may have a more severe reaction on repeated challenge, either accidental, diagnostic, or therapeutic. Such patients may be unresponsive to the usual doses of epinephrine used to treat the allergic reaction.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Two long-term (maximum dosing duration of 18 or 24 months) rat studies and one long-term (maximum dosing duration of 18 months) mouse study, each employing dose levels as high as 300 mg/kg/day or 150 times the maximum recommended human antihypertensive dose,* did not indicate a carcinogenic potential of atenolol. A third (24 month) rat study, employing doses of 500 and 1,500 mg/kg/day (250 and 750 times the maximum recommended human antihypertensive dose*) resulted in increased incidences of benign adrenal medullary tumors in males and females, mammary fibroadenomas in females, and anterior pituitary adenomas and thyroid parafollicular cell carcinomas in males. No evidence of a mutagenic potential of atenolol was uncovered in the dominant lethal test (mouse), in vivo cytogenetics test (Chinese hamster) or Ames test (*S typhimurium*).

Fertility of male or female rats (evaluated at dose levels as high as 200 mg/kg/day or 100 times the maximum recommended human dose*) was unaffected by atenolol administration.

Animal Toxicology: Chronic studies employing oral atenolol performed in animals have revealed the occurrence of vacuolation of epithelial cells of Brunner's glands in the duodenum of both male and female dogs at all tested dose levels of atenolol (starting at 15 mg/kg/day or 7.5 times the maximum recommended human antihypertensive dose*) and increased incidence of atrial degeneration of hearts of male rats at 300 but not 150 mg atenolol/kg/day (150 and 75 times the maximum recommended human antihypertensive dose,* respectively).

Usage in Pregnancy: Pregnancy Category C: Atenolol has been shown to produce a dose- related increase in embryo/fetal resorptions in rats at doses equal to or greater than 50 mg/kg/day or 25 or more times the maximum recommended human antihypertensive dose.* Although similar effects were not seen in rabbits, the compound was not evaluated in rabbits at doses above 25 mg/kg/day or 12.5 times the maximum recommended human antihypertensive dose.* There are no adequate and well-controlled studies in pregnant women. TENORMIN should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

*Based on the maximum dose of 100 mg/day in a 50 kg patient.

Nursing Mothers: Atenolol is excreted in human breast milk at a ratio of 1.5 to 6.8 when compared to the concentration in plasma. Caution should be exercised when TENORMIN is administered to a nursing woman. Clinically significant bradycardia has been reported in breast fed infants. Premature infants, or infants with impaired renal function, may be more likely to develop adverse effects.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: Most adverse effects have been mild and transient.

The frequency estimates in the following table were derived from controlled studies in hypertensive patients in which adverse reactions were either volunteered by the patient (US studies) or elicited, eg, by checklist (foreign studies). The reported frequency of elicited adverse effects was higher for both TENORMIN and placebo-treated patients than when these reactions were volunteered. Where frequency of adverse effects of TENORMIN and placebo is similar, causal relationship to TENORMIN is uncertain.

	Volunteered (US Studies)		Total - Volunteered and Elicited (Foreign + US Studies)	
	Atenolol (n = 164) %	Placebo (n = 206) %	Atenolol (n = 399) %	Placebo (n = 407) %
CARDIOVASCULAR				
Bradycardia	3	0	3	0
Cold Extremities	0	0.5	12	5
Postural Hypotension	2	1	4	5
Leg Pain	0	0.5	3	1
CENTRAL NERVOUS SYSTEM/ NEUROMUSCULAR				
Dizziness	4	1	13	6
Vertigo	2	0.5	2	0.2
Light-headedness	1	0	3	0.7
Tiredness	0.6	0.5	26	13
Fatigue	3	1	6	5
Lethargy	1	0	3	0.7
Drowsiness	0.6	0	2	0.5
Depression	0.6	0.5	12	9
Dreaming	0	0	3	1
GASTROINTESTINAL				
Diarrhea	2	0	3	2
Nausea	4	1	3	1
RESPIRATORY (see WARNINGS)				
Wheeziness	0	0	3	3
Dyspnea	0.6	1	6	4

Acute Myocardial Infarction: In a series of investigations in the treatment of acute myocardial infarction, bradycardia and hypotension occurred more commonly, as expected for any beta blocker, in atenolol-treated patients than in control patients. However, these usually responded to atropine and/or to withholding further dosage of atenolol. The incidence of heart failure was not increased by atenolol. Inotropic agents were infrequently used. The reported frequency of these and other events occurring during these investigations is given in the following table.

In a study of 477 patients, the following adverse events were reported during either intravenous and/or oral atenolol administration:

	Conventional Therapy Plus Atenolol (n=244)		Conventional Therapy Alone (n=233)	
Bradycardia	43	(18%)	24	(10%)
Hypotension	60	(25%)	34	(15%)
Bronchospasm	3	(1.2%)	2	(0.9%)
Heart Failure	46	(19%)	56	(24%)
Heart Block	11	(4.5%)	10	(4.3%)
BBB + Major Axis Deviation	16	(6.6%)	28	(12%)
Supraventricular Tachycardia	28	(11.5%)	45	(19%)
Atrial Fibrillation	12	(5%)	29	(11%)
Atrial Flutter	4	(1.6%)	7	(3%)
Ventricular Tachycardia	39	(16%)	52	(22%)
Cardiac Reinfarction	0	(0%)	6	(2.6%)
Total Cardiac Arrests	4	(1.6%)	16	(6.9%)
Nonfatal Cardiac Arrests	4	(1.6%)	12	(5.1%)
Deaths	7	(2.9%)	16	(6.9%)
Cardiogenic Shock	1	(0.4%)	4	(1.7%)
Development of Ventricular Septal Defect	0	(0%)	2	(0.9%)
Development of Mitral Regurgitation	0	(0%)	2	(0.9%)
Renal Failure	1	(0.4%)	0	(0%)
Pulmonary Emboli	3	(1.2%)	0	(0%)

In the subsequent International Study of Infarct Survival (ISIS-1) including over 16,000 patients of whom 8,037 were randomized to receive TENORMIN treatment, the dosage of intravenous and subsequent oral TENORMIN was either discontinued or reduced for the following reasons:

	Reasons for Reduced Dosage IV Atenolol Reduced Dose (≤ 5mg)*		Oral Partial Dose	
Hypotension/Bradycardia	105	(1.3%)	1168	(14.5%)
Cardiogenic Shock	4	(.04%)	35	(.44%)
Reinfarction	0	(0%)	5	(.06%)
Cardiac Arrest	5	(.06%)	28	(.34%)
Heart Block (> first degree)	5	(.06%)	143	(1.7%)
Cardiac Failure	1	(.01%)	233	(2.9%)
Arrhythmias	3	(.04%)	22	(.27%)
Bronchospasm	1	(.01%)	50	(.62%)

*Full dosage was 10 mg and some patients received less than 10 mg but more than 5 mg.

During postmarketing experience with TENORMIN the following have been reported in temporal relationship to the use of the drug: elevated liver enzymes and or bilirubin, headache, impotence, Peyronie's disease psoriasiform rash or exacerbation of psoriasis, purpura, reversible alopecia, and thrombocytopenia. TENORMIN, like other beta blockers, has been associated with the development of antinuclear antibodies (ANA) and lupus syndrome.

POTENTIAL ADVERSE EFFECTS: In addition, a variety of adverse effects have been reported with other beta-adrenergic blocking agents, and may be considered potential adverse effects of TENORMIN.

Hematologic: Agranulocytosis.

Allergic: Fever, combined with aching and sore throat, laryngospasm, and respiratory distress.

Central Nervous System: Reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation of time and place; short-term memory loss; emotional lability with slightly clouded sensorium; and, decreased performance on neuropsychometrics.

Gastrointestinal: Mesenteric arterial thrombosis, ischemic colitis.

Other: Erythematous rash, Raynaud's phenomenon

Miscellaneous: There have been reports of skin rashes and/or dry eyes associated with the use of beta adrenergic blocking drugs. The reported incidence is small, and in most cases, the symptoms have cleared when treatment was withdrawn. Discontinuance of the drug should be considered if any such reaction is not otherwise explicable. Patients should be closely monitored following cessation of therapy. (SEE DOSAGE AND ADMINISTRATION.)

The oculomucocutaneous syndrome associated with the beta blocker practolol has not been reported with TENORMIN. Furthermore, a number of patients who had previously demonstrated established practolol reactions were transferred to TENORMIN therapy with subsequent resolution or quiescence of the reaction.

OVERDOSAGE: Overdosage with TENORMIN has been reported with patients surviving acute doses as high as 5 g. One death was reported in a man who may have taken as much as 10 g acutely.

The predominant symptoms reported following TENORMIN overdose are lethargy, disorder of respiratory drive, wheezing, sinus pause, and bradycardia. Additionally, common effects associated with overdosage of any beta-adrenergic blocking agent and which might also be expected in TENORMIN overdose are congestive heart failure, hypotension, bronchospasm and/or hypoglycemia.

Treatment of overdose should be directed to the removal of any unabsorbed drug by induced emesis, gastric lavage, or administration of activated charcoal. TENORMIN can be removed from the general circulation by hemodialysis. Other treatment modalities should be employed at the physician's discretion and may include:

BRADYCARDIA: Atropine intravenously. If there is no response to vagal blockade, give isoproterenol cautiously. In refractory cases a transvenous cardiac pacemaker may be indicated.

HEART BLOCK (SECOND OR THIRD DEGREE): Isoproterenol or transvenous cardiac pacemaker.

CARDIAC FAILURE: Digitalize the patient and administer a diuretic. Glucagon has been reported to be useful.

HYPOTENSION: Vasopressors such as dopamine or norepinephrine (levarterenol). Monitor blood pressure continuously.

BRONCHOSPASM: A beta$_2$ stimulant such as isoproterenol or terbutaline and/or aminophylline.

HYPOGLYCEMIA: Intravenous glucose.

Based on the severity of symptoms, management may require intensive support care and facilities for applying cardiac and respiratory support.

DOSAGE AND ADMINISTRATION: Hypertension: The initial dose of TENORMIN is 50 mg given as one tablet a day either alone or added to diuretic therapy. The full effect of this dose will usually be seen within one to two weeks. If an optimal response is not achieved, the dosage should be increased to TENORMIN 100 mg given as one tablet a day. Increasing the dosage beyond 100 mg a day is unlikely to produce any further benefit.

TENORMIN may be used alone or concomitantly with other antihypertensive agents including thiazide-type diuretics, hydralazine, prazosin, and alpha-methyldopa.

Angina Pectoris: The initial dose of TENORMIN is 50 mg given as one tablet a day. If an optimal response is not achieved within one week, the dosage should be increased to TENORMIN 100 mg given as one tablet a day. Some patients may require a dosage of 200 mg once a day for optimal effect.

Twenty-four hour control with once daily dosing is achieved by giving doses larger than necessary to achieve an immediate maximum effect. The maximum early effect on exercise tolerance occurs with doses of 50 to 100 mg, but at these doses the effect at 24 hours is attenuated, averaging about 50% to 75% of that observed with once a day oral doses of 200 mg.

Acute Myocardial Infarction: In patients with definite or suspected acute myocardial infarction, treatment with TENORMIN I.V. Injection should be initiated as soon as possible after the patient's arrival in the hospital and after eligibility is established. Such treatment should be initiated in a coronary care or similar unit immediately after the patient's hemodynamic condition has stabilized. Treatment should begin with the intravenous administration of 5 mg TENORMIN over 5 minutes followed by another 5 mg intravenous injection 10 minutes later. TENORMIN I.V. Injection should be administered under carefully controlled conditions including monitoring of blood pressure, heart rate, and electrocardiogram. Dilutions of TENORMIN I.V. Injection in Dextrose Injection USP, Sodium Chloride Injection USP, or Sodium Chloride and Dextrose Injection may be used. These admixtures are stable for 48 hours if they are not used immediately.

In patients who tolerate the full intravenous dose (10 mg), TENORMIN Tablets 50 mg should be initiated 10 minutes after the last intravenous dose followed by another 50 mg oral dose 12 hours later. Thereafter, TENORMIN can be given orally either 100 mg once daily or 50 mg twice a day for a further 6-9 days or until discharge from the hospital. If bradycardia or hypotension requiring treatment or any other untoward effects occur, TENORMIN should be discontinued.

Data from other beta blocker trials suggest that if there is any question concerning the use of IV beta blocker or clinical estimate that there is a contraindication, the IV beta blocker may be eliminated and patients fulfilling the safety criteria may be given TENORMIN Tablets 50 mg twice daily or 100 mg once a day for at least seven days (if the IV dosing is excluded).

Although the demonstration of efficacy of TENORMIN is based entirely on data from the first seven postinfarction days, data from other beta blocker trials suggest that treatment with beta blockers that are effective in the postinfarction setting may be continued for one to three years if there are no contraindications.

TENORMIN is an additional treatment to standard coronary care unit therapy.

Elderly Patients or Patients with Renal Impairment: TENORMIN is excreted by the kidneys; consequently dosage should be adjusted in cases of severe impairment of renal function. Some reduction in dosage may also be appropriate for the elderly, since decreased kidney function is a physiologic consequence of aging. Atenolol excretion would be expected to decrease with advancing age.

No significant accumulation of TENORMIN occurs until creatinine clearance falls below 35 mL/min/1.73m^2. Accumulation of atenolol and prolongation of its half-life were studied in subjects with creatinine clearance between 5 and 105 mL/min. Peak plasma levels were significantly increased in subjects with creatinine clearances below 30 mL/min.

The following maximum oral dosages are recommended for elderly, renally-impaired patients and for patients with renal impairment due to other causes:

Creatinine Clearance (mL/min/1.73m^2)	Atenolol Elimination Half-Life (h)	Maximum Dosage
15-35	16-27	50 mg daily
<15	>27	25 mg daily

Some renally-impaired or elderly patients being treated for hypertension may require a lower starting dose of TENORMIN: 25 mg given as one tablet a day. If this 25 mg dose is used, assessment of efficacy must be made carefully. This should include measurement of blood pressure just prior to the next dose ("trough" blood pressure) to ensure that the treatment effect is present for a full 24 hours.

Although a similar dosage reduction may be considered for elderly and/or renally-impaired patients being treated for indications other than hypertension, data are not available for these patient populations.

Patients on hemodialysis should be given 25 mg or 50 mg after each dialysis; this should be done under hospital supervision as marked falls in blood pressure can occur.

Cessation of Therapy in Patients with Angina Pectoris: If withdrawal of TENORMIN therapy is planned, it should be achieved gradually and patients should be carefully observed and advised to limit physical activity to a minimum.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

HOW SUPPLIED

TENORMIN Tablets: Tablets of 25 mg atenolol, NDC 0310-0107 (round, flat, uncoated white tablets with "T" debossed on one side and 107 debossed on the other side) are supplied in bottles of 100 tablets.

Tablets of 50 mg atenolol, NDC 0310-0105 (round, flat, uncoated white tablets identified with ICI debossed on one side and 105 debossed on the other side, bisected) are supplied in bottles of 100 tablets and 1000 tablets, and unit dose packages of 100 tablets. These tablets are distributed by ICI Pharma.

Tablets of 100 mg atenolol, NDC 0310-0101 (round, flat, uncoated white tablets with ICI debossed on one side and 101 debossed on the other side) are supplied in bottles of 100 tablets and unit dose packages of 100 tablets. These tablets are distributed by ICI Pharma.

Store at controlled room temperature, 15°-30°C (59°-86°F). Dispense in well-closed, light resistant containers.

TENORMIN I.V. Injection

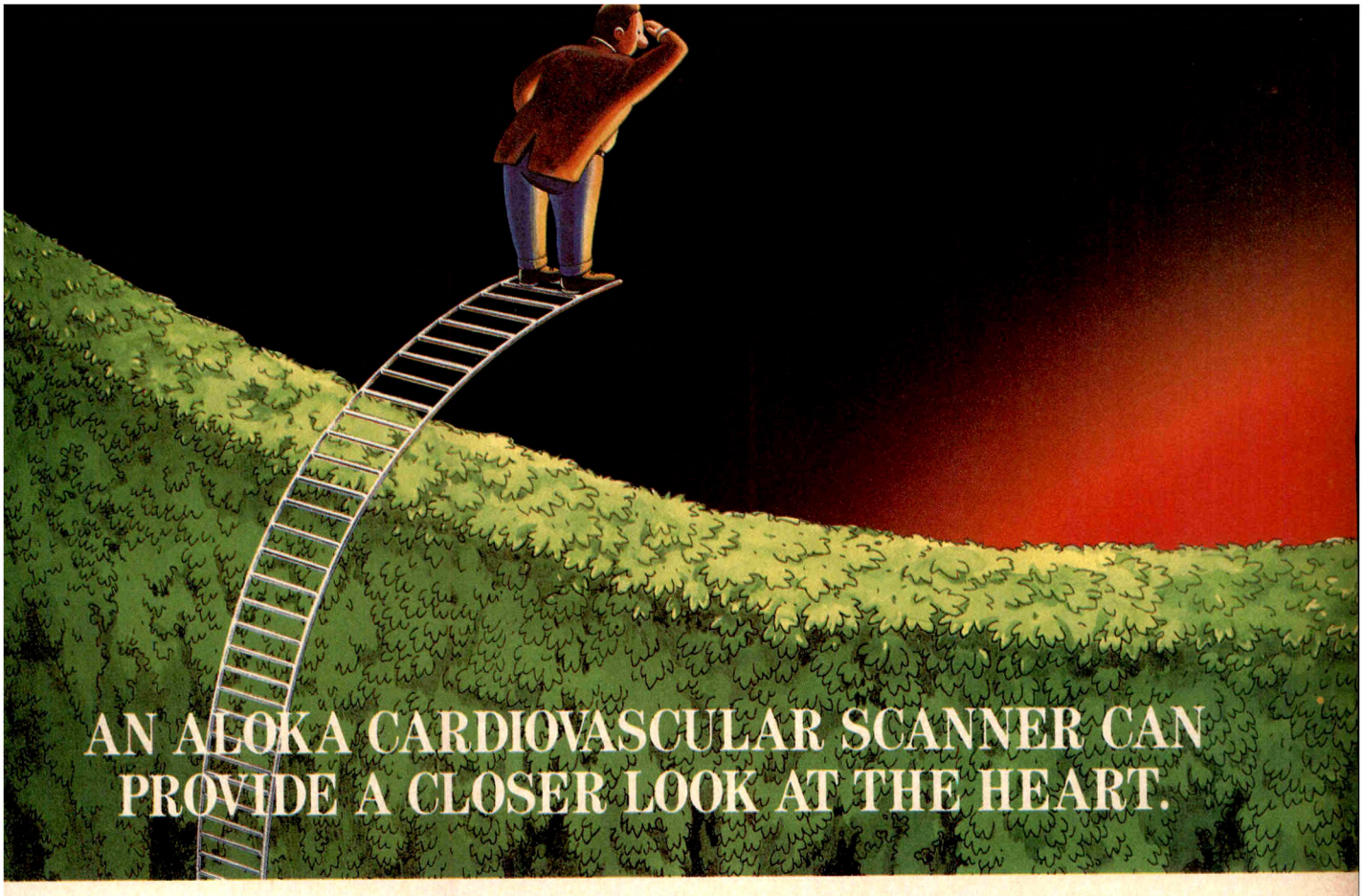
TENORMIN I.V. Injection, NDC 0310-0108, is supplied as 5 mg atenolol in 10 mL ampules of isotonic citrate-buffered aqueous solution.

Protect from light. Keep ampules in outer packaging until time of use. Store at room temperature.

REV X 02/9

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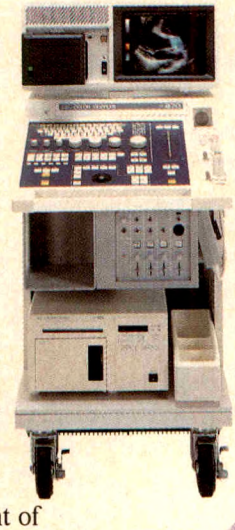
Color Doppler, of course, provides an immediate visual understanding of blood flow. And Aloka's unique color coding system enhances abnormal flows so they are easier to pinpoint.





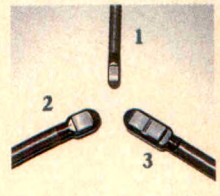
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ARRHYTHMIAS AND CONDUCTION DISTURBANCES

587
Acute Conversion of Paroxysmal Supraventricular Tachycardia with Intravenous Diltiazem
Anne Hamilton Dougherty, Warren M. Jackman, Gerald V. Naccarelli, Karen J. Friday, and Virgil C. Dias, for the IV Diltiazem Study Group

The effectiveness and safety of intravenous diltiazem for the treatment of paroxysmal supraventricular tachycardia (SVT) were examined with a multicenter, randomized, double-blinded, dose-ranging study. Doses of 0.05, 0.15, 0.25 and 0.45 mg/kg of diltiazem were compared with placebo in 87 patients with induced paroxysmal SVT. Prompt conversion to sinus rhythm occurred in 29, 84, 100 and 82% of the diltiazem-treated groups, respectively, compared with 25% of placebo-treated subjects. Paroxysmal SVT cycle length, AH interval, and atrioventricular nodal effective refractory period and node block cycle length lengthened with diltiazem treatment. The most frequently observed adverse effect of diltiazem was hypotension (7 of 63 patients).

593
Lack of Effect of Midazolam on Inducibility of Arrhythmias at Electrophysiologic Study
Alex S. B. Yip, Mark A. McGuire, Lloyd Davis, Davis S. W. Ho, David A. B. Richards, John B. Uther, and David L. Ross

The effects of intravenous midazolam (5 mg) were studied in 20 patients undergoing electrophysiologic studies. Midazolam caused no change in the ease of inducibility of reentrant tachycardias and no change in electrophysiologic variables, apart from a minor decrease in sinus cycle length. It was well-tolerated, had an excellent amnesic effect, and apart from a minor reduction in blood pressure, no significant adverse reaction was noted. In conclusion, midazolam is a suitable drug for routine sedation in patients undergoing electrophysiologic studies.

598
Use-Dependent Electrophysiologic Effects of Amiodarone in Coronary Artery Disease and Inducible Ventricular Tachycardia
Nipavan Chiamvimonvat, L. Brent Mitchell, Anne M. Gillis, D. George Wyse, Robert S. Sheldon, and Henry J. Duff

Amiodarone produces use-dependent block of cardiac sodium channels in vitro. This study assessed whether similar use-dependent block occurred in 19 patients with coronary artery disease and inducible, sustained, monomorphic ventricular tachycardia treated with amiodarone. Beat-to-beat measurements of ventricular-paced QRS durations during 12-beat trains at cycle lengths of 700, 600, 400 and 300 ms were analyzed at a baseline antiarrhythmic drug-free study and after 2 and 10 weeks of amiodarone therapy. At the drug-free study, there were no significant changes in paced QRS durations within the 12-beat trains at any pacing cycle length.

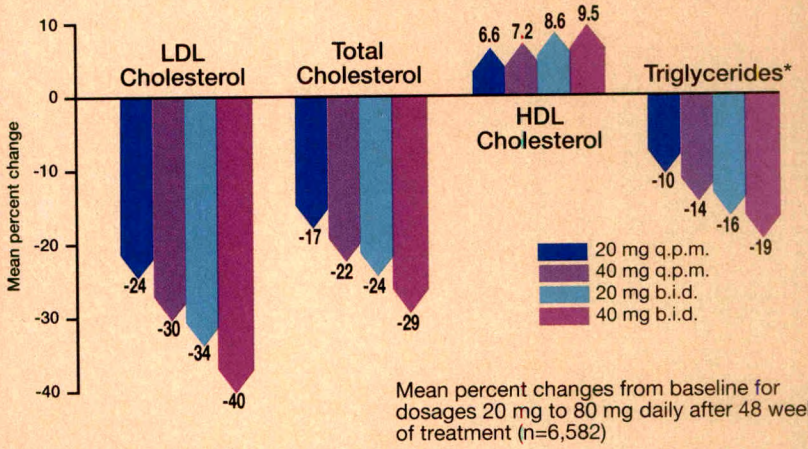
Continued on page A29

The largest U.S. double-blind, placebo-controlled trial of patients with moderate hypercholesterolemia

8,245 patients | 362 clinical sites | 48 weeks

EXPANDED CLINICAL EVALUATION OF LOVASTATIN
THE EXCEL STUDY

Excellent efficacy in lowering LDL and total cholesterol[1]



Mean percent changes from baseline for dosages 20 mg to 80 mg daily after 48 weeks of treatment (n=6,582)

* Triglyceride values are expressed as median changes.

1. Bradford, R.H. et al.: Expanded clinical evaluation of lovastatin (EXCEL) study results: I. Efficacy in modifying plasma lipoproteins and adverse event profile in 8,245 patients with moderate hypercholesterolemia, Arch. Intern. Med. *151*:43-49, January 1991.

For many patients with primary hypercholesterolemia (Types IIa and IIb) when diet and other nondrug therapies are inadequate

MEVACOR®
(LOVASTATIN)

Tablets: 10 mg, 20 mg, 40 mg

Proven in research. Proven in practice.

MSD
MERCK SHARP & DOHME

MEVACOR is contraindicated in patients who are hypersensitive to any component of the medication; in patients with active liver disease or unexplained persistent transaminase elevations; in pregnant or lactating patients; and in women of childbearing age, except when such patients are highly unlikely to conceive.

For complete details on MEVACOR, including cautionary information regarding myopathy, drug interactions, and liver enzyme monitoring, please refer to the Prescribing Information.

For a brief summary of Prescribing Information, please see the next page of this advertisement.

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MEVACOR® *
(LOVASTATIN)

CONTRAINDICATIONS: Hypersensitivity to any component of this medication.

Active liver disease or unexplained persistent elevations of serum transaminases (see WARNINGS).

Pregnancy and lactation.

Atherosclerosis is a chronic process, and the discontinuation of lipid-lowering drugs during pregnancy should have little impact on the outcome of long-term therapy of primary hypercholesterolemia. Moreover, cholesterol and other products of the cholesterol biosynthesis pathway are essential components for fetal development, including synthesis of steroids and cell membranes. Because of the ability of inhibitors of HMG-CoA reductase such as MEVACOR to decrease the synthesis of cholesterol and possibly other products of the cholesterol biosynthesis pathway, MEVACOR may cause fetal harm when administered to a pregnant woman. Therefore, lovastatin is contraindicated during pregnancy. Lovastatin should be administered to women of childbearing age only when such patients are highly unlikely to conceive. If the patient becomes pregnant while taking this drug, lovastatin should be discontinued, and the patient should be apprised of the potential hazard to the fetus.

WARNINGS: *Liver Dysfunction:* Marked persistent increases (to more than 3 times the upper limit of normal) in serum transaminases occurred in 1.9% of adult patients who received lovastatin for at least 1 year in early clinical trials (see ADVERSE REACTIONS). When the drug was interrupted or discontinued in these patients, the transaminase levels usually fell slowly to pretreatment levels. The increases usually appeared 3 to 12 months after the start of therapy with lovastatin and were not associated with jaundice or other clinical signs or symptoms. There was no evidence of hypersensitivity. In the EXCEL study (see CLINICAL PHARMACOLOGY, *Clinical Studies* in the full Prescribing Information), the incidence of marked persistent increases in serum transaminases over 48 weeks was 0.1% for placebo, 0.1% at 20 mg/day, 0.9% at 40 mg/day, and 1.5% at 80 mg/day in patients on lovastatin. However, in post-marketing experience with MEVACOR, symptomatic liver disease has been reported rarely at all dosages (see ADVERSE REACTIONS).

It is recommended that liver function tests be performed during therapy with lovastatin. Serum transaminases, including ALT (SGPT), should be monitored before treatment begins, every 6 weeks during the first 3 months, every 8 weeks during the remainder of the first year, and periodically thereafter (e.g., at approximately 6-month intervals). Special attention should be paid to patients who develop elevated serum transaminase levels, and, in these patients, measurements should be repeated promptly and then performed more frequently. If the transaminase levels show evidence of progression, particularly if they rise to 3 times the upper limit of normal and are persistent, the drug should be discontinued. Liver biopsy should be considered if elevations are persistent beyond the discontinuation of the drug.

The drug should be used with caution in patients who consume substantial quantities of alcohol and/or have a past history of liver disease. Active liver disease or unexplained transaminase elevations are contraindications to the use of lovastatin.

As with other lipid-lowering agents, moderate (less than 3 times the upper limit of normal) elevations of serum transaminases have been reported following therapy with MEVACOR (see ADVERSE REACTIONS). These changes appeared soon after initiation of therapy with MEVACOR, were often transient, were not accompanied by any symptoms, and interruption of treatment was not required.

Skeletal Muscle: **Rhabdomyolysis has been associated with lovastatin therapy alone, when combined with immunosuppressive therapy including cyclosporine in cardiac transplant patients, and when combined in non-transplant patients with either gemfibrozil or lipid-lowering doses (≥1g/day) of nicotinic acid. Some of the affected patients had preexisting renal insufficiency, usually as a consequence of long-standing diabetes. Acute renal failure from rhabdomyolysis has been seen more commonly with the lovastatin-gemfibrozil combination and has also been reported in transplant patients receiving lovastatin plus cyclosporine.**

Rhabdomyolysis with or without renal impairment has been reported in seriously ill patients receiving erythromycin concomitantly with lovastatin. Therefore, patients receiving concomitant lovastatin and erythromycin should be carefully monitored.

Fulminant rhabdomyolysis has been seen as early as 3 weeks after initiation of combined therapy with gemfibrozil and lovastatin, but may be seen after several months. For these reasons, it is felt that, in most subjects who have had an unsatisfactory lipid response to either drug alone, the possible benefits of combined therapy with lovastatin and gemfibrozil do not outweigh the risks of severe myopathy, rhabdomyolysis, and acute renal failure. While it is not known whether this interaction occurs with fibrates other than gemfibrozil, myopathy and rhabdomyolysis have occasionally been associated with the use of other fibrates alone, including clofibrate. Therefore, the combined use of lovastatin with other fibrates should generally be avoided.

Physicians contemplating combined therapy with lovastatin and lipid-lowering doses of nicotinic acid or with immunosuppressive drugs should carefully weigh the potential benefits and risks and should carefully monitor patients for any signs and symptoms of muscle pain, tenderness, or weakness, particularly during the initial months of therapy and during any periods of upward dosage titration of either drug. Periodic creatine phosphokinase (CPK) determinations may be considered in such situations, but there is no assurance that such monitoring will prevent the occurrence of severe myopathy. The monitoring of lovastatin drug and metabolite levels may be considered in transplant patients who are treated with immunosuppressives and lovastatin.

Lovastatin therapy should be temporarily withheld or discontinued in any patient with an acute, serious condition suggestive of a myopathy or having a risk factor predisposing to the development of renal failure secondary to rhabdomyolysis, including: severe acute infection, hypotension, major surgery, trauma, severe metabolic, endocrine, and electrolyte disorders, and uncontrolled seizures.

Myalgia has been associated with lovastatin therapy. Transient, mildly elevated CPK levels are commonly seen in lovastatin-treated patients. However, in early clinical trials, approximately 0.5% of patients developed a myopathy, i.e., myalgia or muscle weakness associated with markedly elevated CPK levels. In the EXCEL study (see CLINICAL PHARMACOLOGY, *Clinical Studies* in the full Prescribing Information), 5 patients (0.1%) taking lovastatin alone (1 at 40 mg q.p.m. and 4 at 40 mg b.i.d.) developed myopathy (muscle symptoms and CPK levels >10 times the upper limit of normal). Myopathy should be considered in any patient with diffuse myalgias, muscle tenderness or weakness, and/or marked elevation of CPK. Patients should be advised to report promptly any unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever. Lovastatin therapy should be discontinued if markedly elevated CPK levels occur or myopathy is diagnosed or suspected.

Most of the patients who have developed myopathy (including rhabdomyolysis) while taking lovastatin were receiving concomitant therapy with immunosuppressive drugs, gemfibrozil, or lipid-lowering doses of nicotinic acid. In clinical trials, about 30% of patients on concomitant immunosuppressive therapy including cyclosporine developed myopathy; the corresponding percentages for gemfibrozil and niacin were approximately 5% and 2%, respectively.

In 6 patients with cardiac transplants taking immunosuppressive therapy including cyclosporine concomitantly with lovastatin 20 mg/day, the average plasma level of active metabolites derived from lovastatin was elevated to approximately 4 times the expected levels. Because of an apparent relationship between increased plasma levels of active metabolites derived from lovastatin and myopathy, the daily dosage in patients taking immunosuppressants should not exceed 20 mg/day (see DOSAGE AND ADMINISTRATION). Even at this dosage, the benefits and risks of using lovastatin in patients taking immunosuppressants should be carefully considered.

PRECAUTIONS: *General:* Before instituting therapy with MEVACOR, an attempt should be made to control hypercholesterolemia with appropriate diet, exercise, and weight reduction in obese patients, and to treat other underlying medical problems (see INDICATIONS AND USAGE in the full Prescribing Information).

Lovastatin may elevate CPK and transaminase levels (see WARNINGS and ADVERSE REACTIONS). This should be considered in the differential diagnosis of chest pain in a patient on therapy with lovastatin.

Homozygous Familial Hypercholesterolemia: MEVACOR is less effective in patients with the rare homozygous familial hypercholesterolemia, possibly because these patients have no functional LDL receptors. MEVACOR appears to be more likely to raise serum transaminases (see ADVERSE REACTIONS) in these homozygous patients.

Information for Patients: Patients should be advised to report promptly any unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever.

Drug Interactions: Immunosuppressive Drugs, Gemfibrozil, Niacin (Nicotinic Acid), Erythromycin: See WARNINGS, *Skeletal Muscle.*

Coumarin Anticoagulants: In a small clinical trial in which lovastatin was administered to warfarin-treated patients, no effect on prothrombin time was detected. However, another HMG-CoA reductase inhibitor has been found to produce a less than 2-second increase in prothrombin time in healthy volunteers receiving low doses of warfarin. Also, bleeding and/or increased prothrombin time have been reported in a few patients taking coumarin anticoagulants concomitantly with lovastatin. It is recommended that in patients taking anticoagulants, prothrombin time be determined before starting lovastatin and frequently enough during early therapy to ensure that no significant alteration of prothrombin time occurs. Once a stable prothrombin time has been documented, prothrombin times can be monitored at the intervals usually recommended for patients on coumarin anticoagulants. If the dose of lovastatin is changed, the same procedure should be repeated. Lovastatin therapy has not been associated with bleeding or with changes in prothrombin time in patients not taking anticoagulants.

Antipyrine: Because lovastatin had no effect on the pharmacokinetics of antipyrine or its metabolites, interactions of other drugs metabolized via the same cytochrome isozymes are not expected.

Propranolol: In normal volunteers, there was no clinically significant pharmacokinetic or pharmacodynamic interaction with concomitant administration of single doses of lovastatin and propranolol.

Digoxin: In patients with hypercholesterolemia, concomitant administration of lovastatin and digoxin resulted in no effect on digoxin plasma concentrations.

Other Concomitant Therapy: Although specific interaction studies were not performed, in clinical studies lovastatin was used concomitantly with beta blockers, calcium channel blockers, diuretics, and nonsteroidal anti-inflammatory drugs (NSAIDs) without evidence of clinically significant adverse interactions.

Endocrine Function: HMG-CoA reductase inhibitors interfere with cholesterol synthesis and as such might theoretically blunt adrenal and/or gonadal steroid production. Results of clinical trials with drugs in this class have been inconsistent with regard to drug effects on basal and reserve steroid levels. However, clinical studies have shown that lovastatin does not reduce basal plasma cortisol concentration or impair adrenal reserve and does not reduce basal plasma testosterone concentration. Another HMG-CoA reductase inhibitor has been shown to reduce the plasma testosterone response to HCG. In the same study, the mean testosterone response to HCG was slightly but not significantly reduced after treatment with lovastatin 40 mg daily for 16 weeks in 21 men. The effects of HMG-CoA reductase inhibitors on male fertility have not been studied in adequate numbers of male patients. The effects, if any, on the pituitary-gonadal axis in premenopausal women are unknown. Patients treated with lovastatin who develop clinical evidence of endocrine dysfunction should be evaluated appropriately. Caution should also be exercised if an HMG-CoA reductase inhibitor or other agent used to lower cholesterol levels is administered to patients also receiving other drugs (e.g., ketoconazole, spironolactone, cimetidine) that may decrease the levels or activity of endogenous steroid hormones.

CNS Toxicity: Lovastatin produced optic nerve degeneration (Wallerian degeneration of retinogeniculate fibers) in clinically normal dogs in a dose-dependent fashion starting at 60 mg/kg/day, a dose that produced mean plasma drug levels about 30 times higher than the mean drug level in humans taking the highest recommended dose (as measured by total enzyme inhibitory activity). Vestibulocochlear Wallerian-like degeneration and retinal ganglion cell chromatolysis were also seen in dogs treated for 14 weeks at 180 mg/kg/day, a dose that resulted in a mean plasma drug level (C_{max}) similar to that seen with the 60 mg/kg/day dose.

CNS vascular lesions, characterized by perivascular hemorrhage and edema, mononuclear cell infiltration of perivascular spaces, perivascular fibrin deposits, and necrosis of small vessels, were seen in dogs treated with lovastatin at a dose of 180 mg/kg/day, a dose that produced plasma drug levels (C_{max}) about 30 times higher than the mean values in humans taking 80 mg/day.

Similar optic nerve and CNS vascular lesions have been observed with other drugs of this class.

Carcinogenesis, Mutagenesis, Impairment of Fertility: In a 21-month carcinogenic study in mice, there was a statistically significant increase in the incidence of hepatocellular carcinomas and adenomas in both males and females at 500 mg/kg/day. This dose produced a total plasma drug exposure 3 to 4 times that of humans given the highest recommended dose of lovastatin (drug exposure was measured as total HMG-CoA reductase inhibitory activity in extracted plasma). Tumor increases were not seen at 20 and 100 mg/kg/day, doses that produced drug exposures of 0.3 to 2 times that of humans at the 80 mg/day dose. A statistically significant increase in pulmonary adenomas was seen in female mice at approximately 4 times the human drug exposure. (Although mice were given 300 times the human dose [HD] on an mg/kg body weight basis, plasma levels of total inhibitory activity were only 4 times higher in mice than in humans given 80 mg of MEVACOR® [Lovastatin].)

There was an increase in incidence of papilloma in the nonglandular mucosa of the stomach of mice beginning at exposures of 1 to 2 times that of humans. The glandular mucosa was not affected. The human stomach contains only glandular mucosa.

In a 24-month carcinogenicity study in rats, there was a positive dose-response relationship for hepatocellular carcinogenicity in males at drug exposures 2 to 7 times that of human exposure at 80 mg/day (doses in rats were 5, 30, and 180 mg/kg/day).

A chemically similar drug in this class was administered to mice for 72 weeks at 25, 100, and 400 mg/kg body weight, which resulted in mean serum drug levels approximately 3, 15, and 33 times higher than the mean human serum drug concentration (as total inhibitory activity) after a 40-mg oral dose. Liver carcinomas were significantly increased in high-dose females and mid- and high-dose males, with a maximum incidence of 90% in males. The incidence of adenomas of the liver was significantly increased in mid- and high-dose females. Drug treatment also significantly increased the incidence of lung adenomas in mid- and high-dose males and females. Adenomas of the Harderian gland (a gland of the eye of rodents) were significantly higher in high-dose mice than in controls.

No evidence of mutagenicity was observed in a microbial mutagen test using mutant strains of *Salmonella typhimurium* with or without rat or mouse liver metabolic activation. In addition, no evidence of damage to genetic material was noted in an *in vitro* alkaline elution assay using rat or mouse hepatocytes, a V-79 mammalian cell forward mutation study, an *in vitro* chromosome aberration study in CHO cells, or an *in vivo* chromosomal aberration assay in mouse bone marrow.

Drug-related testicular atrophy, decreased spermatogenesis, spermatocytic degeneration, and giant cell formation were seen in dogs starting at 20 mg/kg/day. Similar findings were seen with another drug in this class. No drug-related effects on fertility were found in studies with lovastatin in rats. However, in studies with a similar drug in this class, there was decreased fertility in male rats treated for 34 weeks at 25 mg/kg body weight, although this effect was not observed in a subsequent fertility study when this same dose was administered for 11 weeks (the entire cycle of spermatogenesis, including epididymal maturation). In rats treated with this same reductase inhibitor at 180 mg/kg/day, seminiferous tubule degeneration (necrosis and loss of spermatogenic epithelium) was observed. No microscopic changes were observed in the testes from rats of either study. The clinical significance of these findings is unclear.

Pregnancy: Pregnancy Category X: See CONTRAINDICATIONS.

Safety in pregnant women has not been established. Lovastatin has been shown to produce skeletal malformations at plasma levels 40 times the human exposure (for mouse fetus) and 80 times the human exposure (for rat fetus) based on mg/m² surface area (doses were 800 mg/kg/day). No drug-induced changes were seen in either species at multiples of 8 times (rat) or 4 times (mouse) the human exposure based on surface area. No evidence of malformations was noted in rabbits at exposures up to 3 times the human exposure (dose of 15 mg/kg/day, highest tolerated dose). MEVACOR should be administered to women of childbearing potential only when such patients are highly unlikely to conceive and have been informed of the potential hazards. If the woman becomes pregnant while taking MEVACOR, it should be discontinued, and the patient advised again as to the potential hazards to the fetus.

Nursing Mothers: It is not known whether lovastatin is excreted in human milk. Because a small amount of another drug in this class is excreted in human breast milk and because of the potential for serious adverse reactions in nursing infants, women taking MEVACOR should not nurse their infants (see CONTRAINDICATIONS).

Pediatric Use: Safety and effectiveness in children and adolescents have not been established. Because children and adolescents are not likely to benefit from cholesterol lowering for at least a decade and because experience with this drug is limited (no studies in subjects below the age of 20 years), treatment of children with lovastatin is not recommended at this time.

ADVERSE REACTIONS: MEVACOR® (Lovastatin) is generally well tolerated; adverse reactions usually have been mild and transient. Less than 1% of patients were discontinued from controlled clinical studies of up to 14 weeks due to adverse experiences attributable to MEVACOR. About 3% of patients were discontinued from extensions of these studies due to adverse experiences attributable to MEVACOR; about half of these patients were discontinued due to increases in serum transaminases. The median duration of therapy in these extensions was 5.2 years.

In the EXCEL study (see CLINICAL PHARMACOLOGY, *Clinical Studies* in the full Prescribing Information), 4.6% of the patients treated up to 48 weeks were discontinued due to clinical or laboratory adverse experiences that were rated by the investigator as possibly, probably, or definitely related to therapy with MEVACOR. The value for the placebo group was 2.5%.

Clinical Adverse Experiences: Adverse experiences reported in patients (%) treated with MEVACOR (n=613) in controlled clinical studies are: *Gastrointestinal:* constipation, 4.9; diarrhea, 5.5; dyspepsia, 3.9; flatus, 6.4; abdominal pain/cramps, 5.7; heartburn, 1.6; nausea, 4.7; *Musculoskeletal:* muscle cramps, 1.1; myalgia, 2.4; *Nervous System/Psychiatric:* dizziness, 2.0; headache, 9.3; *Skin:* rash/pruritus, 5.2; *Special Senses:* blurred vision, 1.5; dysgeusia, 0.8.

Laboratory Tests: Marked persistent increases of serum transaminases have been noted (see WARNINGS).

About 11% of patients had elevations of creatine phosphokinase (CPK) levels of at least twice the normal value on one or more occasions. The corresponding values for the control agents were cholestyramine, 9%, and probucol, 2%. This was attributable to the noncardiac fraction of CPK. Large increases in CPK have sometimes been reported (see WARNINGS, *Skeletal Muscle*).

Expanded Clinical Evaluation of Lovastatin (EXCEL) Study: Clinical Adverse Experiences: MEVACOR was compared to placebo in 8,245 patients with hypercholesterolemia (total cholesterol 240 to 300 mg/dL [6.2–7.8 mmol/L]) in the randomized, double-blind, parallel, 48-week EXCEL study. Clinical adverse experiences reported as possibly, probably, or definitely drug related in ≥1% of any treatment group are shown in the table below. For no event was the incidence on drug and placebo statistically different.

		MEVACOR			
	Placebo (n=1,663) %	20 mg q.p.m. (n=1,642) %	40 mg q.p.m. (n=1,645) %	20 mg b.i.d. (n=1,646) %	40 mg b.i.d. (n=1,649) %
Body as a Whole					
Asthenia	1.4	1.7	1.4	1.5	1.2
Gastrointestinal					
Abdominal pain	1.6	2.0	2.0	2.2	2.5
Constipation	1.9	2.0	3.2	3.2	3.5
Diarrhea	2.3	2.6	2.4	2.2	2.6
Dyspepsia	1.9	1.3	1.3	1.0	1.6
Flatulence	4.2	3.7	4.3	3.9	4.5
Nausea	2.5	1.9	2.5	2.2	2.2
Musculoskeletal					
Muscle cramps	0.5	0.6	0.8	1.1	1.0
Myalgia	1.7	2.6	1.8	2.2	3.0
Nervous System/ Psychiatric					
Dizziness	0.7	0.7	1.2	0.5	0.5
Headache	2.7	2.6	2.8	2.1	3.2
Skin					
Rash	0.7	0.8	1.0	1.2	1.3
Special Senses					
Blurred vision	0.8	1.1	0.9	0.9	1.2

Other clinical adverse experiences reported as possibly, probably, or definitely drug related in 0.5 to 1% of patients in any drug-treated group are listed below. In all these cases, the incidence on drug and placebo was not statistically different. *Body as a Whole:* chest pain; *Gastrointestinal:* acid regurgitation, dry mouth, vomiting; *Musculoskeletal:* leg pain, shoulder pain, arthralgia; *Nervous System/Psychiatric:* insomnia, paresthesia; *Skin:* alopecia, pruritus; *Special Senses:* eye irritation.

Concomitant Therapy: In controlled clinical studies in which lovastatin was administered concomitantly with cholestyramine, no adverse reactions peculiar to this concomitant treatment were observed. The adverse reactions that occurred were limited to those reported previously with lovastatin or cholestyramine. Other lipid-lowering agents were not administered concomitantly with lovastatin during controlled clinical studies. Preliminary data suggest that the addition of either probucol or gemfibrozil to therapy with lovastatin is not associated with greater reduction in LDL cholesterol than that achieved with lovastatin alone. In uncontrolled clinical studies, most of the patients who have developed myopathy were receiving concomitant therapy with immunosuppressive drugs, gemfibrozil, or niacin (nicotinic acid) (see WARNINGS, *Skeletal Muscle*).

The following effects have been reported with drugs in this class:

Skeletal: myopathy, rhabdomyolysis, arthralgias.

Neurological: dysfunction of certain cranial nerves (including alteration of taste, impairment of extraocular movement, facial paresis), tremor, vertigo, memory loss, paresthesia, peripheral neuropathy, peripheral nerve palsy, anxiety, insomnia, depression.

Hypersensitivity Reactions: an apparent hypersensitivity syndrome has been reported rarely that has included one or more of the following features: anaphylaxis, angioedema, lupus erythematous-like syndrome, polymyalgia rheumatica, vasculitis, purpura, thrombocytopenia, leukopenia, hemolytic anemia, positive ANA, ESR increase, arthritis, arthralgia, urticaria, asthenia, photosensitivity, fever, chills, flushing, malaise, dyspnea, toxic epidermal necrolysis, erythema multiforme, including Stevens-Johnson syndrome.

Gastrointestinal: pancreatitis, hepatitis, including chronic active hepatitis, cholestatic jaundice, fatty change in liver; and rarely, cirrhosis, fulminant hepatic necrosis, and hepatoma; anorexia, vomiting.

Skin: alopecia.

Reproductive: gynecomastia, loss of libido, erectile dysfunction.

Eye: progression of cataracts (lens opacities), ophthalmoplegia.

Laboratory Abnormalities: elevated transaminases, alkaline phosphatase, and bilirubin; thyroid function abnormalities.

OVERDOSAGE: After oral administration of MEVACOR to mice, the median lethal dose observed was >15 g/m².

Five healthy human volunteers have received up to 200 mg of lovastatin as a single dose without clinically significant adverse experiences. A few cases of accidental overdosage have been reported; no patients had any specific symptoms, and all patients recovered without sequelae. The maximum dose taken was 5 to 6 g.

Until further experience is obtained, no specific treatment of overdosage with MEVACOR can be recommended.

The dialyzability of lovastatin and its metabolites in man is not known at present.

DOSAGE AND ADMINISTRATION: The patient should be placed on a standard cholesterol-lowering diet before receiving MEVACOR and should continue on this diet during treatment with MEVACOR. MEVACOR should be given with meals.

The recommended starting dose is 20 mg once a day given with the evening meal. The recommended dosing range is 20 to 80 mg/day in single or divided doses; the maximum recommended dose is 80 mg/day. Adjustments of dosage should be made at intervals of 4 weeks or more. Doses should be individualized according to the patient's response (see Tables I to IV under CLINICAL PHARMACOLOGY, *Clinical Studies* in the full Prescribing Information for dose-response results).

In patients taking immunosuppressive drugs concomitantly with lovastatin (see WARNINGS, *Skeletal Muscle*), therapy should begin with 10 mg of MEVACOR and should not exceed 20 mg/day.

Cholesterol levels should be monitored periodically, and consideration should be given to reducing the dosage of MEVACOR if cholesterol levels fall below the targeted range.

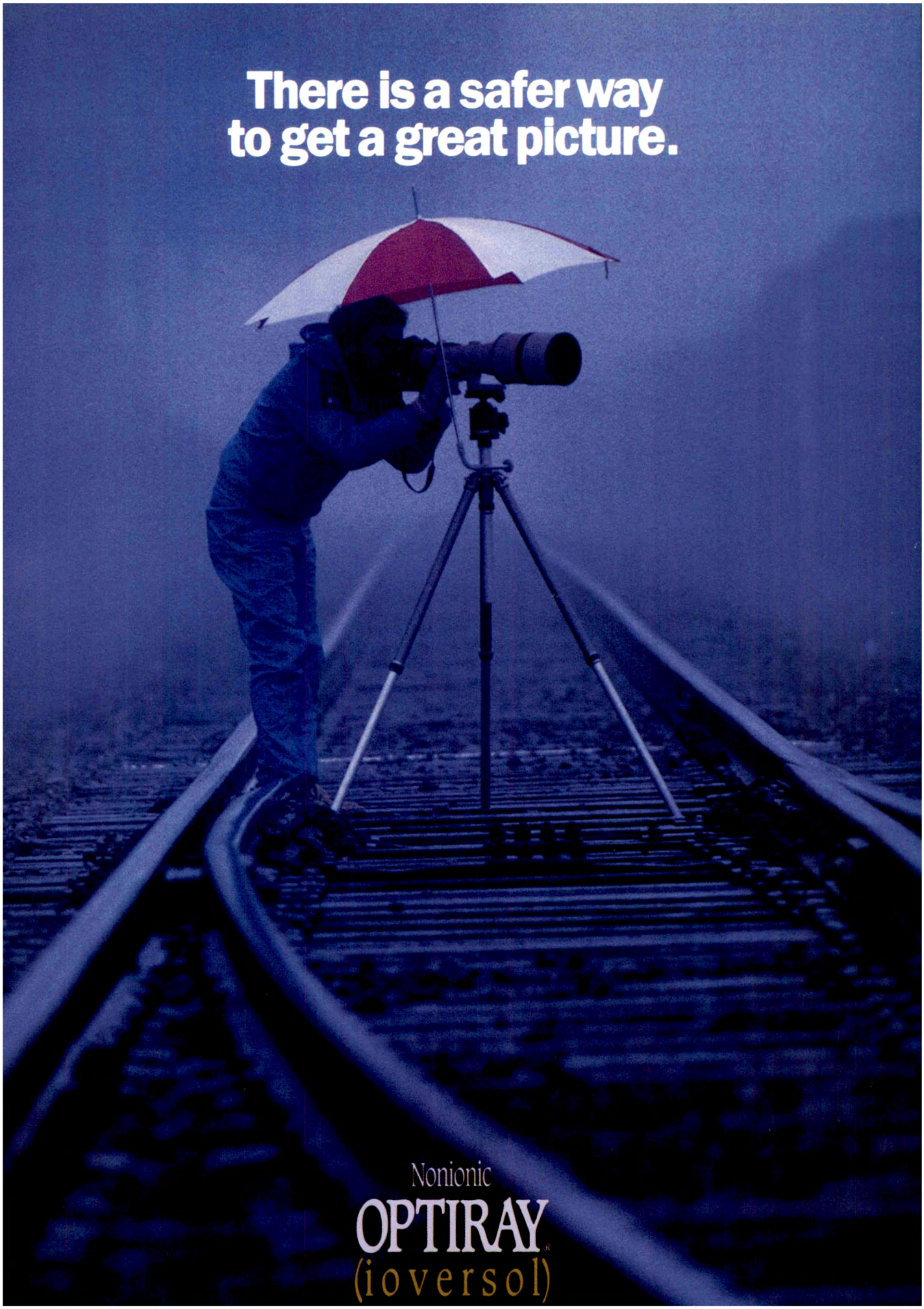
Dosage in Patients with Renal Insufficiency: In patients with severe renal insufficiency (creatinine clearance <30 mL/min), dosage increases above 20 mg/day should be carefully considered and, if deemed necessary, implemented cautiously (see CLINICAL PHARMACOLOGY in the full Prescribing Information and WARNINGS, *Skeletal Muscle*).

For more detailed information, consult your MSD Representative or see the Prescribing Information.

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There is a safer way
to get a great picture.
Nonionic
OPTIRAY
(ioversol)

And a safer way to great cardiac imaging.

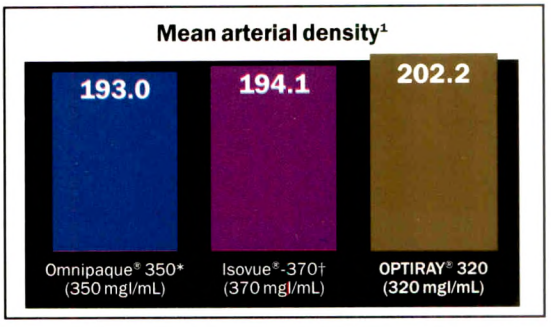


Also available in a 35% concentration: OPTIRAY® 350 (ioversol injection 74%)

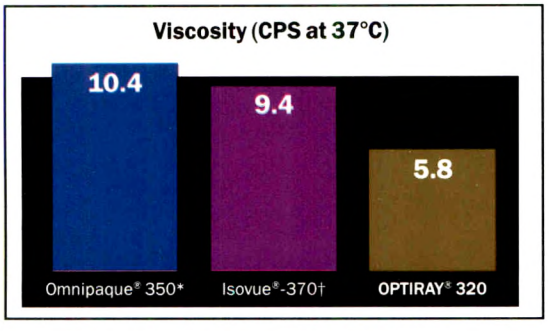
Great cardiac visualization with the safety of lower iodine...

A recent clinical study showed that OPTIRAY® 320 (ioversol injection 68%) provides equivalent image density when compared with contrast agents of higher iodine concentration.[1]

So OPTIRAY® 320 provides a means for reducing the amount of iodine administered with no reduction in overall image quality. And a lower iodine dose may reduce the likelihood of renal dysfunction.[2]

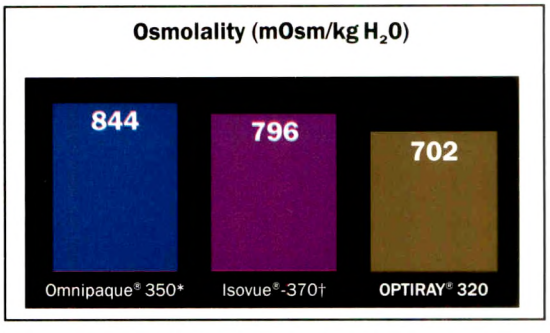


lower viscosity...



The low viscosity and greater flow rate of OPTIRAY® 320 mean easier hand injections and images equivalent to contrast agents with a higher iodine concentration.[1]

and lower osmolality.



OPTIRAY® 320 has the lowest osmolality of these nonionic contrast media.

Sometimes all you need is a little less, to get more.

All nonionic iodinated contrast media currently available inhibit blood coagulation, in vitro, less than ionic contrast media. Clotting has been reported when blood remains in contact with syringes containing nonionic contrast media. Therefore, meticulous intravascular administration technique is necessary to minimize thromboembolic events.

References:

1. Kern MJ, Roth RA, Aguirre FV, Beauman G, Vogel R. Effect of viscosity and iodine concentration of nonionic radiographic contrast media on coronary arteriography in patients. *Am Heart J.* 1992; 123:160-165. 2. Gomes AS, Baker JD, Martin-Paredero V, et al. Acute renal dysfunction after major arteriography. *AJR.* 1985; 145:1249-1253.

*Omnipaque® (iohexol) — Winthrop Pharmaceuticals
†Isovue® (iopamidol) — E.R. Squibb & Sons, Inc.

Please see the following page for a brief summary of prescribing information.

Nonionic
OPTIRAY®
(ioversol)

A safer way to great imaging

OPTIRAY® 160 240 320 350 (Ioversol Injection)

DESCRIPTION: Each milliliter of OPTIRAY 160 (ioversol injection 34%) provides 339 mg of ioversol with 3.6 mg of tromethamine as a buffer and 0.2 mg of edetate calcium disodium as a stabilizer. OPTIRAY 160 provides 16% (160 mg/mL) organically bound iodine.

Each milliliter of OPTIRAY 240 (ioversol injection 51%) provides 509 mg of ioversol with 3.6 mg of tromethamine as a buffer and 0.2 mg of edetate calcium disodium as a stabilizer. OPTIRAY 240 provides 24% (240 mg/mL) organically bound iodine.

Each milliliter of OPTIRAY 320 (ioversol injection 68%) provides 678 mg of ioversol with 3.6 mg of tromethamine as a buffer and 0.2 mg of edetate calcium disodium as a stabilizer. OPTIRAY 320 provides 32% (320 mg/mL) organically bound iodine.

Each milliliter of OPTIRAY 350 (ioversol injection 74%) provides 741 mg of ioversol with 3.6 mg of tromethamine as a buffer and 0.2 mg of edetate calcium disodium as a stabilizer. OPTIRAY 350 provides 35% (350 mg/mL) organically bound iodine.

CONTRAINDICATIONS: None.

WARNINGS: Nonionic iodinated contrast media inhibit blood coagulation, in vitro, less than ionic contrast media. Clotting has been reported when blood remains in contact with syringes containing nonionic contrast media.

Serious, rarely fatal, thromboembolic events causing myocardial infarction and stroke have been reported during angiographic procedures with both ionic and nonionic contrast media. Therefore, meticulous intravascular administration technique is necessary, particularly during angiographic procedures, to minimize thromboembolic events. Numerous factors, including length of procedure, catheter and syringe material, underlying disease state and concomitant medications may contribute to the development of thromboembolic events. For these reasons, meticulous angiographic techniques are recommended including close attention to guidewire and catheter manipulation, use of manifold systems and/or three-way stopcocks, frequent catheter flushing with heparinized saline solutions and minimizing the length of the procedure. The use of plastic syringes in place of glass syringes has been reported to decrease but not eliminate the likelihood of in vitro clotting.

Serious or fatal reactions have been associated with the administration of iodine-containing radiopaque media. It is of utmost importance to be completely prepared to treat any contrast medium reaction.

As with any contrast medium, serious neurologic sequelae, including permanent paralysis, can occur following cerebral arteriography, selective spinal arteriography and arteriography of vessels supplying the spinal cord. A cause-effect relationship to the contrast medium has not been established since the patients' pre-existing condition and procedural technique are causative factors in themselves. The arterial injection of a contrast medium should never be made following the administration of vasopressors since they strongly potentiate neurologic effects.

Caution must be exercised in patients with severely impaired renal function, combined renal and hepatic disease, severe thyrotoxicosis, myelomatosis, or anuria, particularly when large doses are administered.

Intravascularly administered iodine-containing radiopaque media are potentially hazardous in patients with multiple myeloma or other paraproteinemia, particularly in those with therapeutically resistant anuria. Myeloma occurs most commonly in persons over age 40. Although neither the contrast agent nor dehydration has been proved separately to be the cause of anuria in myelomatous patients, it has been speculated that the combination of both may be causative. The risk in myelomatous patients is not a contraindication to the procedure; however, special precautions, including maintenance of normal hydration and close monitoring, are required. Partial dehydration in the preparation of these patients prior to injection is not recommended since this may predispose the patient to precipitation of the myeloma protein.

Administration of radiopaque materials to patients known or suspected of having pheochromocytoma should be performed with extreme caution. If, in the opinion of the physician, the possible benefits of such procedures outweigh the considered risks, the procedures may be performed; however, the amount of radiopaque medium injected should be kept to an absolute minimum. The blood pressure should be assessed throughout the procedure, and measures for treatment of a hypertensive crisis should be available.

Contrast media may promote sickling in individuals who are homozygous for sickle cell disease when administered intravascularly.

Reports of thyroid storm following the intravascular use of iodinated radiopaque agents in patients with hyperthyroidism or with an autonomously functioning thyroid nodule, suggest that this additional risk be evaluated in such patients before use of any contrast medium.

PRECAUTIONS: *General:* Diagnostic procedures which involve the use of iodinated intravascular contrast agents should be carried out under the direction of personnel skilled and experienced in the particular procedure to be performed. A fully equipped emergency cart, or equivalent supplies and equipment, and personnel competent in recognizing and treating adverse reactions of all types should always be available. Since severe delayed reactions have been known to occur, emergency facilities and competent personnel should be available for at least 30 to 60 minutes after administration.

Preparatory dehydration is dangerous and may contribute to acute renal failure in patients with advanced vascular disease, diabetic patients, and in susceptible non-diabetic patients (often elderly with pre-existing renal disease). *Patients should be well hydrated prior to and following the administration of OPTIRAY.*

The possibility of a reaction, including serious, life-threatening, fatal, anaphylactoid or cardiovascular reactions, should always be considered (See ADVERSE REACTIONS). Increased risk is associated with a history of previous reaction to a contrast medium, a known sensitivity to iodine and known allergies (i.e., bronchial asthma, hay fever and food allergies) or hypersensitivities.

The occurrence of severe idiosyncratic reactions has prompted the use of several pretesting methods. However, pretesting cannot be relied upon to predict severe reactions and may itself be hazardous to the patient. It is suggested that a thorough medical history with emphasis on allergy and hypersensitivity, prior to the injection of any contrast medium, may be more accurate than pretesting in predicting potential adverse reactions. A positive history of allergies or hypersensitivity does not arbitrarily contraindicate the use of a contrast agent when a diagnostic procedure is thought essential, but caution should be exercised. Premedication with antihistamines or corticosteroids to avoid or minimize possible allergic reactions in such patients should be considered. Reports indicate that such pretreatment does not prevent serious life-threatening reactions, but may reduce both their incidence and severity.

General anesthesia may be indicated in the performance of some procedures in selected patients; however, a higher incidence of adverse reactions has been reported in these patients, and may be attributable to the inability of the patient to identify untoward symptoms or to the hypotensive effect of anesthesia which can prolong the circulation time and increase the duration of exposure to the contrast agent.

In angiographic procedures, the possibility of dislodging plaques or damaging or perforating the vessel wall should be considered during catheter manipulations and contrast medium injection. Test injections to insure proper catheter placement are suggested.

Angiography should be avoided whenever possible in patients with homocystinuria because of the risk of inducing thrombosis and embolism.

Patients with congestive heart failure should be observed for several hours following the procedure to detect delayed hemodynamic disturbances which may be associated with a transitory increase in the circulating osmotic load.

Selective coronary arteriography should be performed only in selected patients and those in whom the expected benefits outweigh the procedural risk. The inherent risks of angiocardiography in patients with chronic pulmonary emphysema must be weighed against the necessity for performing this procedure.

Extreme caution during injection of a contrast medium is necessary to avoid extravasation. This is especially important in patients with severe arterial or venous disease.

Drug Interactions: Renal toxicity has been reported in a few patients with liver dysfunction who were given oral cholecystographic agents followed by intravascular contrast agents. Administration of any intravascular contrast agent should therefore be postponed in patients who have recently received a cholecystographic contrast agent.

Other drugs should not be mixed with ioversol injection.

Drug Laboratory Test Interactions: The results of PBI and radioactive iodine uptake studies, which depend on iodine estimation, will not accurately reflect thyroid function for up to 16 days following administration of iodinated contrast media. However, thyroid function tests not depending on iodine estimations, e.g., T3 resin uptake and total or free thyroxine (T4) assays are not affected.

Carcinogenesis, Mutagenesis, Impairment of Fertility: No long term animal studies have been performed to evaluate carcinogenic potential. However, animal studies suggest that this drug is not mutagenic and does not affect fertility.

Pregnancy Category B: No teratogenic effects attributable to ioversol have been observed in teratology studies performed in animals. There are, however, no adequate and well controlled studies in pregnant women. It is not known whether ioversol crosses the placental barrier or reaches fetal tissues. However, many injectable contrast agents cross the placental barrier in humans and appear to enter fetal tissue passively. Because animal teratology studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed. X-ray procedures involve a certain risk related to the exposure of the fetus.

Nursing Mothers: It is not known whether ioversol is excreted in human milk. However, many injectable contrast agents are excreted unchanged in human milk. Although it has not been established that serious adverse reactions occur in nursing infants, caution should be exercised when intravascular contrast media are administered to nursing women because of potential adverse reactions, and consideration should be given to temporarily discontinuing nursing.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: Adverse reactions following the use of OPTIRAY formulations are usually mild to moderate, of short duration and resolve spontaneously (without treatment). However, serious, life-threatening and fatal reactions, mostly of cardiovascular origin, have been associated with the administration of iodine-containing contrast media.

Injections of contrast media are often associated with sensations of warmth and pain. In controlled double-blind clinical studies, significantly less warmth and pain were associated with the injection of OPTIRAY than with iothalamate meglumine, diatrizoate meglumine, and diatrizoate meglumine and diatrizoate sodium.

When OPTIRAY was used for coronary arteriography and ventriculography in double-blind clinical trials, electrocardiographic and hemodynamic changes occurred with less frequency and severity with ioversol injection than with diatrizoate meglumine and diatrizoate sodium.

Following coronary artery and left ventricular injection, electrocardiographic parameters were affected less with OPTIRAY (ioversol injection) than with diatrizoate meglumine and diatrizoate sodium injection. These parameters included the following: bradycardia, tachycardia, T-wave amplitude, ST depression and ST elevation.

OPTIRAY has also been shown to cause fewer changes in cardiac function and systemic blood pressure than conventional ionic media. These include cardiac output, left ventricular systolic and end-diastolic pressure, right ventricular systolic and pulmonary artery systolic pressures and decreases in systolic and diastolic blood pressures.

The following table of incidence of reactions is based upon clinical trials with OPTIRAY formulations in over 1466 patients. This listing includes all adverse reactions which were coincidental to the administration of ioversol regardless of their direct attributability to the drug or the procedure. Adverse reactions are listed by organ system and in decreasing order of occurrence. Significantly more severe reactions are listed before others in a system regardless of frequency.

Adverse Reactions

System	> 1%	≤ 1%
Cardiovascular	none	angina pectoris hypotension blood pressure fluctuation arterial spasm bradycardia conduction defect false aneurysm hypertension transient arrhythmia vascular trauma
Digestive	none	nausea vomiting
Nervous	none	cerebral infarct headache blurred vision vertigo lightheadedness vasovagal reaction disorientation paresthesia dysphasia muscle spasm syncope visual hallucination
Respiratory	none	laryngeal edema pulmonary edema sneezing nasal congestion coughing shortness of breath hypoxia
Skin	none	periorbital edema urticaria facial edema flush pruritus
Miscellaneous	none	extravasation hematoma shaking chills bad taste general pain

Regardless of the contrast medium employed, the overall incidence of serious adverse reaction is higher with coronary arteriography than with other procedures. Cardiac decompensation, serious arrhythmias, myocardial ischemia or myocardial infarction may occur during coronary arteriography and left ventriculography.

General Adverse Reactions to Contrast Media

The following adverse reactions are possible with any parenterally administered iodinated contrast medium. Severe life-threatening reactions and fatalities, mostly of cardiovascular origin, have occurred. Most deaths occur during injection or 5 to 10 minutes later; the main feature being cardiac arrest with cardiovascular disease as the main aggravating factor. Isolated reports of hypotensive collapse and shock are found in the literature. Based upon clinical literature, reported deaths from the administration of conventional iodinated contrast agents range from 6.6 per 1 million (0.00066 percent) to 1 in 10,000 patients (0.01 percent).

The reported incidence of adverse reactions to contrast media in patients with a history of allergy is twice that of the general population. Patients with a history of previous reactions to a contrast medium are three times more susceptible than other patients. However, sensitivity to contrast media does not appear to increase with repeated examinations.

Adverse reactions to injectable contrast media fall into two categories: chemotoxic reactions and idiosyncratic reactions.

Chemotoxic reactions result from the physicochemical properties of the contrast medium, the dose and the speed of injection. All hemodynamic disturbances and injuries to organs or vessels perfused by the contrast medium are included in this category.

Idiosyncratic reactions include all other reactions. They occur more frequently in patients 20 to 40 years old. Idiosyncratic reactions may or may not be dependent on the dose injected, the speed of injection, the mode of injection and the radiographic procedure. Idiosyncratic reactions are subdivided into minor, intermediate and severe. The minor reactions are self-limited and of short duration; the severe reactions are life-threatening and treatment is urgent and mandatory.

In addition to the adverse reactions reported for ioversol, the following additional adverse reactions have been reported with the use of other contrast agents and are possible with any water soluble, iodinated contrast agent.

Nervous: convulsions, aphasia, paralysis, visual field losses which are usually transient but may be permanent, coma and death.

Cardiovascular: angioneurotic edema, peripheral edema, vasodilation, thrombosis and rarely thrombophlebitis, disseminated intravascular coagulation and shock.

Skin: maculopapular rash, erythema, conjunctival symptoms, ecchymosis and tissue necrosis.

Respiratory: choking, dyspnea, wheezing which may be an initial manifestation of more severe and infrequent reactions including asthmatic attack, laryngospasm and bronchospasm, apnea and cyanosis. Rarely these allergic-type reactions can progress into anaphylaxis with loss of consciousness, coma, severe cardiovascular disturbances and death.

Miscellaneous: hyperthermia, temporary anuria or other nephropathy.

Other reactions may also occur with the use of any contrast agent as a consequence of the procedural hazard; these include hemorrhage or pseudoaneurysms at the puncture site, brachial plexus palsy following axillary artery injections, chest pain, myocardial infarction, and transient changes in hepatorenal chemistry tests. Arterial thrombosis, displacement of arterial plaques, venous thrombosis, dissection of the coronary vessels and transient sinus arrest are rare complications.

In cerebral arteriography, cardiovascular reactions that may occur with some frequency are bradycardia and either an increase or decrease in systemic blood pressure. Neurological reactions that may occur are: seizures, drowsiness, transient paresis, and mild disturbances in vision.

Central nervous system reactions with OPTIRAY in controlled clinical studies in cerebral arteriography that were considered drug-related and occurred with frequencies greater than 1% were: headache, bradycardia, blood pressure fluctuation, disorientation, nausea and vertigo.

In aortography, depending on the technique employed, the risks of this procedure also include the following: injury to the aorta and neighboring organs, pleural puncture, renal damage including infarction and acute tubular necrosis with oliguria and anuria, retroperitoneal hemorrhage from the translumbar approach and spinal cord injury and pathology associated with the syndrome of transverse myelitis. Under conditions of slowed aortic circulation there is an increased likelihood for aortography to cause muscle spasm. Occasional serious neurologic complications, including paraplegia, have also been reported in patients with aortoiliac obstruction, femoral artery obstruction, abdominal compression, hypotension, hypertension, spinal anesthesia, and injection of vasopressors to increase contrast. In these patients the concentration, volume, and number of repeat injections of the medium should be maintained at a minimum with appropriate intervals between injections. The position of the patient and catheter tip should be carefully monitored.

Entry of a large aortic dose into the renal artery may cause, even in the absence of symptoms, albuminuria, hematuria, and an elevated creatinine and urea nitrogen. Rapid and complete return of function usually follows.

There were no cardiovascular system reactions with OPTIRAY in controlled clinical studies in coronary arteriography with left ventriculography that were considered drug-related and occurred with a frequency greater than 1%.

PRECAUTIONS FOR SPECIFIC PROCEDURES:

Cerebral Arteriography

Extreme caution is advised in patients with advanced arteriosclerosis, severe hypertension, cardiac decompensation, senility, recent cerebral thrombosis or embolism, and migraine.

Peripheral Arteriography

Pulsation should be present in the artery to be injected. In thromboangiitis obliterans, or ascending infection associated with severe ischemia, angiography should be performed with extreme caution, if at all.

Coronary Arteriography and Left Ventriculography

Mandatory prerequisites to the procedure are specialized personnel, ECG monitoring apparatus and adequate facilities for immediate resuscitation and cardioversion. Electrocardiograms and vital signs should be routinely monitored throughout the procedure.

Venography

Special care is required when venography is performed in patients with suspected thrombosis, phlebitis, severe ischemic disease, local infection or a totally obstructed venous system. In order to minimize extravasation during injection, fluoroscopy is recommended.

Intravenous Digital Subtraction Angiography

In addition to the general precautions previously described, the risks associated with IV DSA include those usually attendant with catheter procedures and include intramural injections, vessel dissection and tissue extravasation. The potential risk is reduced when small test injections of contrast medium are made under fluoroscopic observation to insure that the catheter tip is properly positioned and, in the case of peripheral placement, that the vein is of adequate size.

Patient motion, including respiration and swallowing, can result in misregistration leading to image degradation and non-diagnostic studies.

OVERDOSAGE: The adverse effects of overdosage are life-threatening and affect mainly the pulmonary and cardiovascular system. Treatment of an overdosage is directed toward the support of all vital functions, and prompt institution of symptomatic therapy.

Ioversol does not bind to plasma or serum protein and is therefore, dialyzable.

The intravenous LD_{50} values (gl/kg) for ioversol in animals were: 17 (mice), and 15 (rats).

DOSAGE AND ADMINISTRATION: Details on dosage are provided in the package insert. CONSULT FULL PACKAGE INSERT BEFORE USE.

MALLINCKRODT *Cardiology*

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However, after 2 and 10 weeks of amiodarone therapy, progressive prolongation of paced QRS durations occurred over the 12-beat trains at pacing cycle lengths of 600, 400 and 300 ms ($p < 0.05$). Significant changes in QRS duration were not observed at a pacing cycle length of 700 ms. The magnitudes of QRS prolongation were similar after 2 and 10 weeks of amiodarone therapy. In conclusion, use-dependent prolongation in QRS duration occurs at rapid pacing cycle lengths in humans receiving amiodarone.

605

Reproducibility of a Symptomatic Response to Upright Tilt in Young Patients with Unexplained Syncope

Frank A. Fish, Janette F. Strasburger, and D. Woodrow Benson, Jr.

The reproducibility of response to 90° upright tilt testing was evaluated in 21 patients with recurrent syncope and a positive tilt test. Repeat tilt was performed 20 to 25 minutes after the initial symptomatic response. Eighteen of the 21 patients had a persistently abnormal physiologic response, but 7 patients experienced milder symptoms or remained entirely asymptomatic during repeat tilt. Time to symptom onset correlated poorly between initial and repeat tilt. The correlation was better for minimal heart rate and minimal systolic blood pressure, but with a tendency toward attenuation during repeat tilt. It is concluded that immediate repeat tilt testing may be insufficiently reproducible to assess response to acute therapeutic interventions.

610

Circadian Rhythm of Heart Rate Variability in Survivors of Cardiac Arrest

Heikki V. Huikuri, Markku K. Linnaluoto, Tapio Seppänen, K.E. Juhani Airaksinen, Kenneth M. Kessler, Juha T. Takkunen, and Robert J. Myerburg

Heart rate (HR) variability and its circadian pattern were compared in 24 survivors of out-of-hospital cardiac arrest and 24 matched control patients. Survivors of cardiac arrest had significantly lower 24-hour average standard deviation of RR intervals than control patients ($p < 0.001$), and the 24-hour mean high-frequency spectral area was also lower in survivors of cardiac arrest than in control patients ($p < 0.01$). A single cosinor analysis revealed a significant circadian rhythm of HR variability in both groups with the acrophase of standard deviation of RR intervals and high-frequency spectral area occurring between 3 and 6 A.M., which was followed by an abrupt decrease in HR variability after arousal. Thus, HR variability is impaired in survivors of cardiac arrest with coronary artery disease compared with matched control patients. A very low HR variability is observed in the morning, which corresponds to the time period at which the incidence of sudden cardiac death is highest.

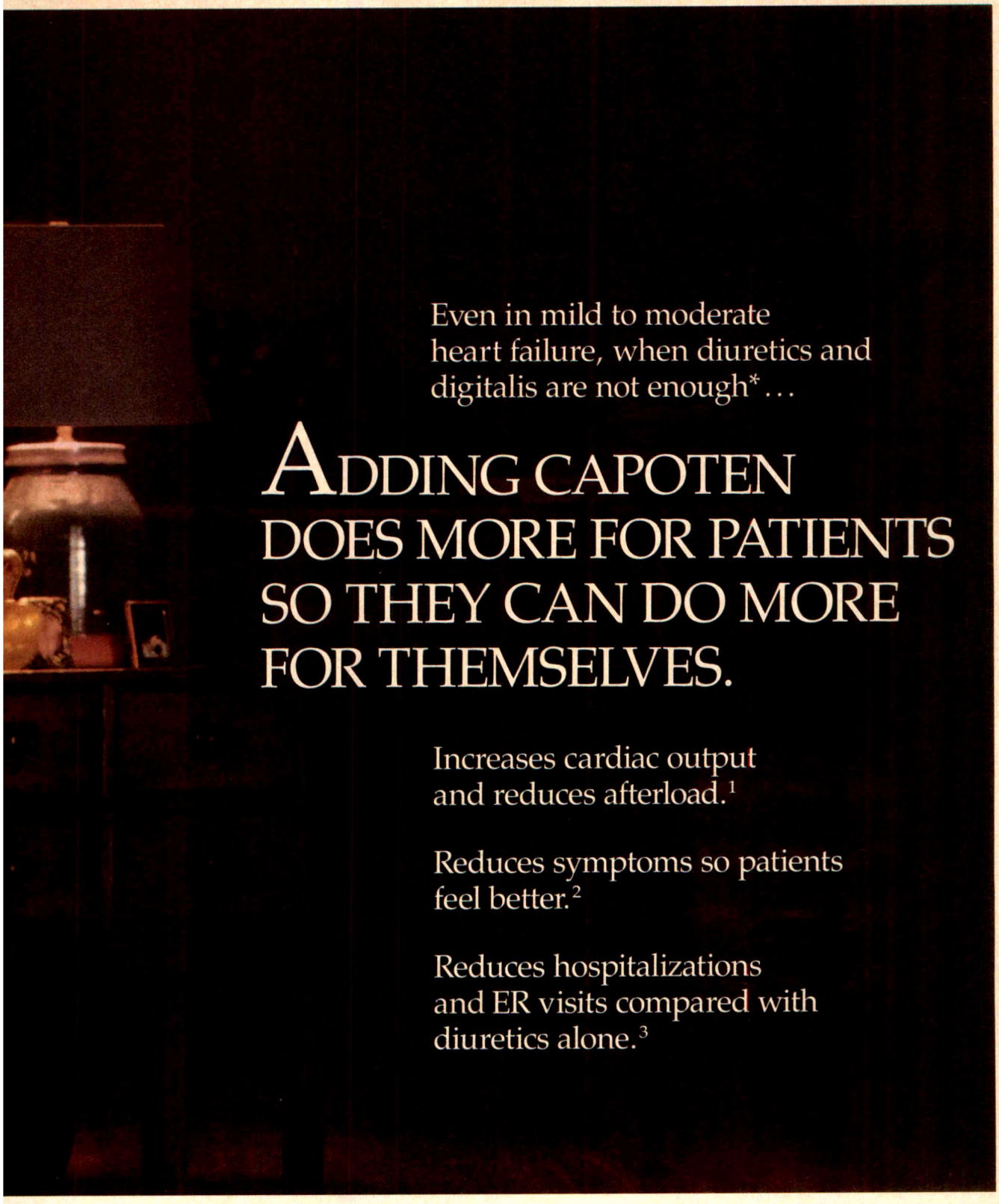
Continued on page A33



CAPOTEN is contraindicated in patients who are hypersensitive to this product. Angioedema has been reported in patients receiving ACE inhibitors.

***CAPOTEN should generally be added to diuretics and digitalis except when digitalis use is poorly tolerated or otherwise not feasible; add CAPOTEN when patients have not responded adequately.**

Please see brief summary, including the **boxed WARNING regarding Use in Pregnancy,** on the last page of this ad.



Even in mild to moderate heart failure, when diuretics and digitalis are not enough*...

ADDING CAPOTEN DOES MORE FOR PATIENTS SO THEY CAN DO MORE FOR THEMSELVES.

Increases cardiac output and reduces afterload.[1]

Reduces symptoms so patients feel better.[2]

Reduces hospitalizations and ER visits compared with diuretics alone.[3]

IN HEART FAILURE

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USE IN PREGNANCY

When used in pregnancy during the second and third trimesters, ACE inhibitors can cause injury and even death to the developing fetus. When pregnancy is detected, CAPOTEN should be discontinued as soon as possible. **See WARNINGS: Fetal/Neonatal Morbidity and Mortality.**

CONTRAINDICATIONS: CAPOTEN is contraindicated in patients who are hypersensitive to this product or any other angiotensin-converting enzyme inhibitor (e.g., a patient who has experienced angioedema during therapy with any other ACE inhibitor).

WARNINGS: Angioedema: Angioedema involving the extremities, face, lips, mucous membranes, tongue, glottis or larynx has been seen in patients treated with ACE inhibitors, including captopril. If angioedema involves the tongue, glottis or larynx, airway obstruction may occur and be fatal. Emergency therapy, including but not necessarily limited to, subcutaneous administration of a 1:1000 solution of epinephrine should be promptly instituted.

Neutropenia / Agranulocytosis: Neutropenia (< 1000/mm³) with myeloid hypoplasia has resulted from use of captopril. About half of the neutropenic patients developed systemic or oral cavity infections or other features of the syndrome of agranulocytosis. The risk of neutropenia is dependent on the clinical status of the patient:

In clinical trials in patients with hypertension who have normal renal function (serum creatinine less than 1.6 mg/dL and no collagen vascular disease), neutropenia has been seen in one patient out of over 8,600 exposed. In patients with some degree of renal failure (serum creatinine at least 1.6 mg/dL) but no collagen vascular disease, the risk in clinical trials was about 1 per 500. Doses were relatively high in these patients, particularly in view of their diminished renal function. In patients with collagen vascular diseases (e.g., systemic lupus erythematosus, scleroderma) and impaired renal function, neutropenia occurred in 3.7% of patients in clinical trials. While none of the over 750 patients in formal clinical trials of heart failure developed neutropenia, it has occurred during the subsequent clinical experience. Of reported cases, about half had serum creatinine ≥ 1.6 mg/dL and more than 75% received procainamide. In heart failure, it appears that the same risk factors for neutropenia are present.

Neutropenia has appeared usually within 3 months after starting therapy, associated with myeloid hypoplasia and frequently accompanied by erythroid hypoplasia and decreased numbers of megakaryocytes (e.g., hypoplastic bone marrow and pancytopenia); anemia and thrombocytopenia were sometimes seen. Neutrophils generally returned to normal in about 2 weeks after captopril was discontinued, and serious infections were limited to clinically complex patients. About 13% of the cases of neutropenia have ended fatally, but almost all fatalities were in patients with serious illness, having collagen vascular disease, renal failure, heart failure or immunosuppressant therapy, or a combination of these complicating factors. **Evaluation of the hypertensive or heart failure patient should always include assessment of renal function.** If captopril is used in patients with impaired renal function, white blood cell and differential counts should be evaluated prior to starting treatment and at approximately 2-week intervals for about 3 months, then periodically. In patients with collagen vascular disease or who are exposed to other drugs known to affect the white cells or immune response, particularly when there is impaired renal function, captopril should be used only after an assessment of benefit and risk, and then with caution. All patients treated with captopril should be told to report any signs of infection (e.g., sore throat, fever). If infection is suspected, perform white cell counts without delay. Since discontinuation of captopril and other drugs has generally led to prompt return of the white count to normal, upon confirmation of neutropenia (neutrophil count < 1000/mm³) withdraw captopril and closely follow the patient's course.

Proteinuria: Total urinary proteins > 1 g per day were seen in about 0.7% of patients on captopril. About 90% of affected patients had evidence of prior renal disease or received high doses (> 150 mg/day), or both. The nephrotic syndrome occurred in about one-fifth of proteinuric patients. In most cases, proteinuria subsided or cleared within 6 months whether or not captopril was continued. The BUN and creatinine were seldom altered in proteinuric patients. Since most cases of proteinuria occurred by the 8th month of therapy with captopril, patients with prior renal disease or those receiving captopril at doses > 150 mg per day, should have urinary protein estimates (dip-stick on 1st morning urine) before therapy, and periodically thereafter.

Hypotension: Excessive hypotension was rarely seen in hypertensive patients but is a possible consequence of captopril use in salt/volume depleted persons (such as those treated vigorously with diuretics), patients with heart failure or those patients undergoing renal dialysis. (See PRECAUTIONS: Drug Interactions.) In heart failure, where the blood pressure was either normal or low, transient decreases in mean blood pressure > 20% were recorded in about half of the patients. This transient hypotension is more likely to occur after any of the first several doses and is usually well tolerated, although rarely it has been associated with arrhythmia or conduction defects. A starting dose of 6.25 or 12.5 mg tid may minimize the hypotensive effect. Patients should be followed closely for the first 2 weeks of treatment and whenever the dose of captopril and/or diuretic is increased.

BECAUSE OF THE POTENTIAL FALL IN BLOOD PRESSURE IN THESE PATIENTS, THERAPY SHOULD BE STARTED UNDER VERY CLOSE MEDICAL SUPERVISION.

Fetal / Neonatal Morbidity and Mortality: ACE inhibitors can cause fetal and neonatal morbidity and death when administered to pregnant women. Several dozen cases have been reported in the world literature. When pregnancy is detected, ACE inhibitors should be discontinued as soon as possible.

The use of ACE inhibitors during the second and third trimesters of pregnancy has been associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death. Oligohydramnios has also been reported, presumably resulting from decreased fetal renal function; oligohydramnios in this setting has been associated with fetal limb contractures, craniofacial deformation, and hypoplastic lung development. Prematurity, intrauterine growth retardation, and patent ductus arteriosus have also been reported, although it is not clear whether these occurrences were due to the ACE-inhibitor exposure.

These adverse effects do not appear to have resulted from intrauterine ACE-inhibitor exposure that has been limited to the first trimester. Mothers whose embryos and fetuses are exposed to ACE inhibitors only during the first trimester should be so informed. Nonetheless, when patients become pregnant, physicians should make every effort to discontinue the use of captopril as soon as possible.

Rarely (probably less often than once in every thousand pregnancies), no alternative to ACE inhibitors will be found. In these rare cases, the mothers should be apprised of the potential hazards to their fetuses, and serial ultrasound examinations should be performed to assess the intraamniotic environment.

If oligohydramnios is observed, captopril should be discontinued unless it is considered life-saving for the mother. Contraction stress testing (CST), a non-stress test (NST), or biophysical profiling (BPP) may be appropriate, depending upon the week of pregnancy. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury.

Infants with histories of *in utero* exposure to ACE inhibitors should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion. Exchange transfusion or dialysis may be required as a means of reversing hypotension and/or substituting for disordered renal function. While captopril may be removed from the adult circulation by hemodialysis, there is inadequate data concerning the effectiveness of hemodialysis for removing it from the circulation of neonates or children. Peritoneal dialysis is not effective for removing captopril; there is no information concerning exchange transfusion for removing captopril from the general circulation.

When captopril was given to rabbits at doses about 0.8 to 70 times (on a mg/kg basis) the maximum recommended human dose, low incidences of craniofacial malformations were seen. No teratogenic effects of captopril were seen in studies of pregnant rats and hamsters. On a mg/kg basis, the doses used were up to 150 times (in hamsters) and 625 times (in rats) the maximum recommended human dose.

PRECAUTIONS: General: *Impaired Renal Function*—Hypertension–Some hypertensive patients with renal disease, particularly those with severe renal artery stenosis, have developed increases in BUN and serum creatinine. It may be necessary to reduce captopril dosage and/or discontinue diuretic. For some of these patients, normalization of blood pressure and maintenance of adequate renal perfusion may not be possible. Heart Failure—About 20% of patients develop stable elevations of BUN and serum creatinine > 20% above normal or baseline upon long-term treatment. Less than 5% of patients, generally with severe preexisting renal disease, required discontinuation due to progressively increasing creatinine. (See DOSAGE AND ADMINISTRATION, ADVERSE REACTIONS: Altered Laboratory Findings.) *Hyperkalemia:* Elevations in serum potassium have been observed in some patients treated with ACE inhibitors, including captopril. When treated with ACE inhibitors, patients at risk for the development of hyperkalemia include those with: renal insufficiency; diabetes mellitus; and those using concomitant potassium-sparing diuretics, potassium supplements or potassium-containing salt substitutes; or other drugs associated with increases in serum potassium. (See PRECAUTIONS: Drug Interactions; ADVERSE REACTIONS: Altered Laboratory Findings.) *Cough*—Cough has been reported with the use of ACE inhibitors. Characteristically, the cough is nonproductive, persistent and resolves after discontinuation of therapy. ACE inhibitor-induced cough should be considered as part of the differential diagnosis of cough. *Valvular Stenosis*—A theoretical concern, for risk of decreased coronary perfusion, has been noted regarding vasodilator treatment in patients with aortic stenosis due to decreased afterload reduction. *Surgery/Anesthesia*—If hypotension occurs during surgery or anesthesia, and is considered due to the effects of captopril, it is correctable by volume expansion.

Pregnancy. Female patients of childbearing age should be told about the consequences of second- and third-trimester exposure to ACE inhibitors, and they should also be told that these consequences do not appear to have resulted from intrauterine ACE-inhibitor exposure that has been limited to the first trimester. These patients should be asked to report pregnancies to their physicians as soon as possible.

Drug Interactions: *Hypotension–Patients on Diuretic Therapy*—Precipitous reduction of blood pressure may occasionally occur within the 1st hour after administration of the initial captopril dose in patients on diuretics, especially those recently placed on diuretics, and those on severe dietary salt restriction or dialysis. This possibility can be minimized by either discontinuing the diuretic or increasing the salt intake about 1 week prior to initiation of captopril therapy or by initiating therapy with small doses (6.25 or 12.5 mg). Alternatively, provide medical supervision for at least 1 hour after the initial dose.

Agents Having Vasodilator Activity—In heart failure patients, vasodilators should be administered with caution.

Agents Causing Renin Release—Captopril's effect will be augmented by antihypertensive agents that cause renin release.

Agents Affecting Sympathetic Activity—The sympathetic nervous system may be especially important in supporting blood pressure in patients receiving captopril alone or with diuretics. Beta-adrenergic blocking drugs add some further antihypertensive effect to captopril, but the overall response is less than additive. Therefore, use agents affecting sympathetic activity (e.g., ganglionic blocking agents or adrenergic neuron blocking agents) with caution.

Agents Increasing Serum Potassium—Give potassium-sparing diuretics or potassium supplements only for documented hypokalemia, and then with caution, since they may lead to a significant increase of serum potassium. Use potassium-containing salt substitutes with caution.

Inhibitors of Endogenous Prostaglandin Synthesis—Indomethacin and other nonsteroidal anti-inflammatory agents may reduce the antihypertensive effect of captopril, especially in low renin hypertension.

Lithium—Increased serum lithium levels and symptoms of lithium toxicity have been reported in patients receiving concomitant lithium and ACE inhibitor therapy. These drugs should be coadministered with caution and frequent monitoring of serum lithium levels is recommended. If a diuretic is also used, it may increase the risk of lithium toxicity.

Drug/Laboratory Test Interaction: Captopril may cause a false-positive urine test for acetone.

Carcinogenesis, Mutagenesis and Impairment of Fertility: Two-year studies with doses of 50 to 1350 mg/kg/day in mice and rats failed to show any evidence of carcinogenic potential. Studies in rats have revealed no impairment of fertility.

Pregnancy Categories C (first trimester) and D (second and third trimesters)
See WARNINGS: Fetal/Neonatal Morbidity and Mortality.

Nursing Mothers: Concentrations of captopril in human milk are approximately one percent of those in maternal blood. Because of the potential for serious adverse reactions in nursing infants from captopril, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of CAPOTEN to the mother. (See PRECAUTIONS: Pediatric Use.)

Pediatric Use: Safety and effectiveness in children have not been established. There is limited experience reported in the literature with the use of captopril in the pediatric population; dosage, on a weight basis, was generally reported to be comparable to or less than that used in adults.

Infants, especially newborns, may be more susceptible to the adverse hemodynamic effects of captopril. Excessive, prolonged and unpredictable decreases in blood pressure and associated complications, including oliguria and seizures, have been reported.

CAPOTEN (captopril) should be used in children only if other measures for controlling blood pressure have not been effective.

ADVERSE REACTIONS: Reported incidences are based on clinical trials involving approximately 7000 patients.

Renal: About 1 of 100 patients developed proteinuria (see WARNINGS). Renal insufficiency, renal failure, nephrotic syndrome, polyuria, oliguria, and urinary frequency in 1 to 2 of 1000 patients.

Hematologic: Neutropenia/agranulocytosis has occurred (see WARNINGS). Anemia, thrombocytopenia, and pancytopenia have been reported.

Dermatologic: Rash, (usually maculopapular, rarely urticarial), often with pruritus, and sometimes with fever and eosinophilia, in about 4 to 7 of 100 patients (depending on renal status and dose), usually during the 1st 4 weeks of therapy. Pruritus, without rash, in about 2 of 100 patients. A reversible associated pemphigoid-like lesion, and photosensitivity, have also been reported. Flushing or pallor in 2 to 5 of 1000 patients.

Cardiovascular: Hypotension may occur; see WARNINGS and PRECAUTIONS [Drug Interactions] for discussion of hypotension with captopril therapy. Tachycardia, chest pain, and palpitations each in about 1 of 100 patients. Angina pectoris, myocardial infarction, Raynaud's syndrome, and congestive heart failure each in 2 to 3 of 1000 patients.

Dysgeusia: Approximately 2 to 4 (depending on renal status and dose) of 100 patients developed a diminution or loss of taste perception; taste impairment is reversible and usually self-limited even with continued drug use (2 to 3 months).

Angioedema: Angioedema involving the extremities, face, lips, mucous membranes, tongue, glottis or larynx has been reported in approximately one in 1000 patients. Angioedema involving the upper airways has caused fatal airway obstruction. (See WARNINGS.)

Cough: Cough has been reported in 0.5-2% of patients treated with captopril in clinical trials (see PRECAUTIONS: General: *Cough*).

The following have been reported in about 0.5 to 2 percent of patients but did not appear at increased frequency compared to placebo or other treatments used in controlled trials: gastric irritation, abdominal pain, nausea, vomiting, diarrhea, anorexia, constipation, aphthous ulcers, peptic ulcer, dizziness, headache, malaise, fatigue, insomnia, dry mouth, dyspnea, cough, alopecia, paresthesias.

Other clinical adverse effects reported since the drug was marketed are listed below by body system. In this setting, an incidence or causal relationship cannot be accurately determined.

General: Asthenia, gynecomastia.
Cardiovascular: Cardiac arrest, cerebrovascular accident/insufficiency, rhythm disturbances, orthostatic hypotension, syncope.
Dermatologic: Bullous pemphigus, erythema multiforme (including Stevens-Johnson syndrome), exfoliative dermatitis.
Gastrointestinal: Pancreatitis, glossitis, dyspepsia.
Hematologic: Anemia, including aplastic and hemolytic.
Hepatobiliary: Jaundice, hepatitis, including rare cases of necrosis, cholestasis.
Metabolic: Symptomatic hyponatremia.
Musculoskeletal: Myalgia, myasthenia.
Nervous/Psychiatric: Ataxia, confusion, depression, nervousness, somnolence.
Respiratory: Bronchospasm, eosinophilic pneumonitis, rhinitis.
Special Senses: Blurred vision.
Urogenital: Impotence.

As with other ACE inhibitors, a syndrome has been reported which may include: fever, myalgia, arthralgia, interstitial nephritis, vasculitis, rash or other dermatologic manifestations, eosinophilia and an elevated ESR.

Fetal/Neonatal Morbidity and Mortality
See WARNINGS: Fetal/Neonatal Morbidity and Mortality.

Altered Laboratory Findings: *Serum Electrolytes:* Hyperkalemia: small increases in serum potassium, especially in patients with renal impairment (see PRECAUTIONS).

Hyponatremia: particularly in patients receiving a low sodium diet or concomitant diuretics.

BUN/Serum Creatinine: Transient elevations of BUN or serum creatinine especially in volume or salt depleted patients or those with renovascular hypertension may occur. Rapid reduction of long-standing or markedly elevated blood pressure can result in decreases in the glomerular filtration rate and, in turn, lead to increases in BUN or serum creatinine.

Hematologic: A positive ANA has been reported.

Liver Function Tests: Elevations of liver transaminases, alkaline phosphatase, and serum bilirubin have occurred.

OVERDOSAGE: Primary concern is correction of hypotension. Volume expansion with an I.V. infusion of normal saline is the treatment of choice for restoration of blood pressure.

While captopril may be removed from the adult circulation by hemodialysis, there is inadequate data concerning the effectiveness of hemodialysis for removing it from the circulation of neonates or children. Peritoneal dialysis is not effective for removing captopril; there is no information concerning exchange transfusion for removing captopril from the general circulation.

DOSAGE AND ADMINISTRATION: CAPOTEN (captopril) should be taken one hour before meals. In hypertension, CAPOTEN may be dosed bid or tid. Dosage must be individualized; see DOSAGE AND ADMINISTRATION section of package insert for detailed information regarding dosage in hypertension and in heart failure. Because CAPOTEN (captopril) is excreted primarily by the kidneys, dosage adjustments are recommended for patients with impaired renal function.

Consult package insert before prescribing CAPOTEN (captopril).

HOW SUPPLIED: Available in tablets of: 12.5 mg in bottles of 100 and 1000; 25 mg in bottles of 100 and 1000; 50 mg in bottles of 100 and 1000; 100 mg of bottles of 100; and in UNIMATIC® unit-dose packs of 100 tablets. (J3-658Z)

References: 1. Physicians' Desk Reference®, 45th ed, Oradell, NJ. Medical Economics Co Inc, 1991, pp 2141-2143. **2.** Captopril Multicenter Research Group: A placebo-controlled trial of captopril in refractory chronic congestive heart failure. *JACC* 2:755-763, 1983. **3.** The Captopril-Digoxin Multicenter Research Group: Comparative effects of therapy with captopril and digoxin in patients with mild to moderate heart failure. *JAMA* 259:539-544, 1988.

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0522-517

Issued: May 1992

616
Use of Telemetry Functions in the Assessment of Implanted Antitachycardia Device Efficacy
David Newman, Paul Dorian, Eugene Downar, Louise Harris, Douglas Cameron, Menashe Waxman, Robert Hamilton, Richard Gow, and Judy Hardy

Twenty patients received an investigational, implanted antitachycardia pacemaker-defibrillator system. The telemetry capabilities of the device enabled reconstruction of the RR intervals and logic-circuit signals of all therapies delivered over 10.1 ± 5.5 months of follow-up. Tachycardia acceleration occurred in 5.3% of 874 pace termination attempts. Three cases of inappropriate sensing due to loss of electrode integrity were accurately diagnosed from outpatient device telemetry, and an absence of correlation between symptoms and device use was seen.

CONGESTIVE HEART FAILURE

622
Exercise Hyperventilation Chronic Heart Failure, and Its Relation to Functional Capacity and Hemodynamics
Marco Metra, Livio Dei Cas, Gaia Panina, and Odoardo Visioli

The slope of the relation between minute ventilation (VE) and carbon dioxide production (VCO_2) was evaluated as an index of exercise ventilatory response in 26 normal sedentary men and 68 patients with chronic heart failure studied with maximal bicycle cardiopulmonary exercise testing and right-sided cardiac catheterization (33 patients). The slope of VE/VCO_2 could be calculated using data from all the exercise tests and the first 60% of exercise duration. VE/VCO_2 was significantly, although weakly, related to peak exercise work load, oxygen consumption and ventilatory threshold, several peak exercise hemodynamic parameters and peak exercise dead space/tidal volume ratio. With use of multivariate analysis, the only independent determinants of the slope were peak exercise dead space/tidal volume ratio and cardiac index. Thus, in patients with heart failure, exercise hyperventilation can contribute to the impairment of functional capacity and can be considered as a compensatory response to abnormal hemodynamics and lung blood distribution to keep arterial blood gas concentrations normal during exercise.

629
Effects of Acute and Chronic Ibopamine Administration on Resting and Exercise Hemodynamics, Plasma Catecholamines and Functional Capacity of Patients with Chronic Congestive Heart Failure
Livio Dei Cas, Marco Metra, and Odoardo Visioli

The effects of acute and chronic administration of ibopamine were evaluated in 25 patients with chronic heart failure caused by idiopathic or postinfarction cardiomyopathy. Resting and exercise hemodynamics, exercise capacity and plasma catecholamines were assessed before and after acute and chronic (2 months) administration of either placebo or ibopa-

mine (100 mg 3 times daily), using a double-blind, parallel, placebo-controlled design. One patient was withdrawn from each treatment group for worsening heart failure; New York Heart Association functional class improved in 4 patients treated with ibopamine and in 1 on placebo; furosemide dose could be decreased in 4 on ibopamine and in no patient on placebo. Ibopamine administration induced a significant increase in both resting and exercise cardiac indexes and in stroke volume index, with a reduction in systemic vascular resistance. These hemodynamic changes were maintained also after chronic therapy, with no evidence of tolerance development. No significant change in the other hemodynamic parameters was noted. Exercise capacity (evaluated as maximal exercise duration and oxygen consumption at peak exercise, and ventilatory threshold) was not significantly changed. Resting and exercise norepinephrine plasma levels were significantly reduced after both acute and chronic ibopamine administration, with no significant change in plasma epinephrine.

VALVULAR HEART DISEASE

635
Exclusion of Coronary Artery Disease by Exercise Thallium-201 Tomography in Patients with Aortic Valve Stenosis

Markku Kupari, Kari S. Virtanen, Heikki Turto, Matti Viitasalo, Matti Mänttäri, Magnus Lindroos, Eero Koskela, Hannu Leinonen, Sinikka Pohjola-Sintonen, and Juhani Heikkilä

The use of exercise thallium-201 tomography to the exclusion of coronary artery disease (CAD) was studied in 44 patients with aortic valve stenosis (AS) undergoing cardiac catheterization. Twenty-one patients had significant CAD (≥50% diameter stenosis in ≥1 coronary artery), and 23 had either a normal angiogram (n = 17) or mild stenoses (n = 6). Each patient with significant CAD had an abnormal thallium-201 tomogram, either a strictly segmental perfusion defect (n = 19), or a patchy nonsegmental abnormality (n = 2); however, 10 of 23 patients free of significant CAD also had the same results. Thus, the sensitivity and specificity of an abnormal scintigram were 100 and 57%, respectively. Patients with false abnormal scintigrams had more severe AS and more angiographically nonsignificant CAD than those with true normal findings. It is concluded that a fully normal exercise thallium-201 tomogram excludes significant CAD in patients with AS, and that false abnormal findings are related to the presence of critical AS and angiographically mild coronary stenoses.

641
Immediate Effects of Percutaneous Transvenous Mitral Commissurotomy on Pulmonary Hemodynamics at Rest and During Exercise in Mitral Stenosis

Mitsuru Ohshima, Masaru Yamazoe, Yusuke Tamura, Taku Matsubara, Masataka Suzuki, Yutaka Igarashi, Yasuhiko Tanabe, Yuko Yamazaki, Sen Koyama, Toshio Yamaguchi, Motoko Mito, Tohru Izumi, Akira Shibata, Tsutomu Miida, Hirotaka Oda, Tetsuro Toeda, and Norio Higuma

Hemodynamics were evaluated during exercise in 33 patients with mitral stenosis who underwent percutaneous transvenous mitral commissuroto-

Continued on page A36

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my (PTMC) using the Inoue balloon. Each patient underwent a symptom-limited supine ergometer exercise test before and on the day after PTMC. Mitral valve area increased 1.1 ± 0.3 to 1.9 ± 0.4 cm^2. Mean mitral pressure gradient decreased 12 ± 5 to 6 ± 2 mm Hg. Pulmonary arterial pressure decreased and cardiac index increased both at rest and during exercise after PTMC. Before PTMC, total pulmonary resistance and pulmonary arteriolar resistance increased during exercise. After PTMC, total pulmonary resistance still increased during exercise. However, pulmonary arteriolar resistance did not change during exercise in patients with a mitral valve area ≥ 1.5 cm^2, whereas it increased in patients with an area <1.5 cm^2. An enlarged mitral valve area ≥ 1.5 cm^2, which may prevent pulmonary vasoconstriction and permits more increase in pulmonary blood flow during exercise, is considered a good result immediately after PTMC.

CARDIOMYOPATHY

645
Comparison of the Cardiotoxicity of Ethanol in Women Versus Men

Markku Kupari and Pekka Koskinen

The female heart has been claimed to be resistant to the cardiotoxicity of alcohol abuse. M-mode and Doppler echocardiography were performed to study left ventricular (LV) anatomy and function in 14 chronic female alcoholics and in 2 age-matched control groups consisting of 17 healthy women and 22 alcoholic men. Compared with healthy women, the female alcoholics had statistically significant impairments of LV fractional shortening and several Doppler indexes of LV filling. Although the alcoholic men had a longer duration of heavy drinking and a higher systolic blood pressure, there were no statistically significant differences between alcoholic men and women either in LV anatomy normalized to body area or in indexes of LV function. It is concluded that subclinical LV dysfunction is a common occurrence even in female alcoholics. The cardiotoxicity of ethanol does not spare the female heart.

651
Altered Cardiac Hemodynamic and Electrical State in Normal Sinus Rhythm After Chronic Dual-Chamber Pacing for Relief of Left Ventricular Outflow Obstruction in Hypertrophic Cardiomyopathy

Dorothea McAreavey and Lameh Fananapazir

Changes in hemodynamics and in the surface 12-lead and signal-averaged electrocardiograms in sinus rhythm were studied at baseline and after dual-chamber (DDD) pacing for 12 weeks in 18 patients with obstructive hypertrophic cardiomyopathy. Obstruction to left ventricular outflow was reduced significantly (by 56 ± 10 mm Hg) after DDD pacing ($p < 0.001$), as well as in normal sinus rhythm. There were significant bidirectional changes in amplitudes of the R, S and T waves on the 12-lead electrocardiograms in leads II, III and aVF and the anteroseptal leads. There were also bidirectional changes in the duration and root-mean-square of the

Continued on page A39

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BRIEF SUMMARY

CARDIZEM® CD (diltiazem hydrochloride) Capsules

CARDIZEM® SR (diltiazem hydrochloride) Sustained Release Capsules

CONTRAINDICATIONS

CARDIZEM is contraindicated in (1) patients with sick sinus syndrome except in the presence of a functioning ventricular pacemaker, (2) patients with second- or third-degree AV block except in the presence of a functioning ventricular pacemaker, (3) patients with hypotension (less than 90 mm Hg systolic), (4) patients who have demonstrated hypersensitivity to the drug, and (5) patients with acute myocardial infarction and pulmonary congestion documented by X-ray on admission.

WARNINGS

1. Cardiac Conduction. CARDIZEM prolongs AV node refractory periods without significantly prolonging sinus node recovery time, except in patients with sick sinus syndrome. This effect may rarely result in abnormally slow heart rates (particularly in patients with sick sinus syndrome) or second- or third-degree AV block (13 of 3,007 patients or 0.43%). Concomitant use of diltiazem with beta-blockers or digitalis may result in additive effects on cardiac conduction. A patient with Prinzmetal's angina developed periods of asystole (2 to 5 seconds) after a single dose of 60 mg of diltiazem.

2. Congestive Heart Failure. Although diltiazem has a negative inotropic effect in isolated animal tissue preparations, hemodynamic studies in humans with normal ventricular function have not shown a reduction in cardiac index nor consistent negative effects on contractility (dp/dt). An acute study of oral diltiazem in patients with impaired ventricular function (ejection fraction 24% ± 6%) showed improvement in indices of ventricular function without significant decrease in contractile function (dp/dt). Worsening of congestive heart failure has been reported in patients with preexisting impairment of ventricular function. Experience with the use of CARDIZEM in combination with beta-blockers in patients with impaired ventricular function is limited. Caution should be exercised when using this combination.

3. Hypotension. Decreases in blood pressure associated with CARDIZEM therapy may occasionally result in symptomatic hypotension.

4. Acute Hepatic Injury. Mild elevations of transaminases with and without concomitant elevation in alkaline phosphatase and bilirubin have been observed in clinical studies. Such elevations were usually transient and frequently resolved even with continued diltiazem treatment. In rare instances, significant elevations in enzymes such as alkaline phosphatase, LDH, SGOT, SGPT, and other phenomena consistent with acute hepatic injury have been noted. These reactions tended to occur early after therapy initiation (1 to 8 weeks) and have been reversible upon discontinuation of drug therapy. The relationship to CARDIZEM is uncertain in some cases, but probable in some. (See PRECAUTIONS.)

PRECAUTIONS

General. CARDIZEM is extensively metabolized by the liver and excreted by the kidneys and in bile. As with any drug given over prolonged periods, laboratory parameters should be monitored at regular intervals. The drug should be used with caution in patients with impaired renal or hepatic function. In subacute and chronic dog and rat studies designed to produce toxicity, high doses of diltiazem were associated with hepatic damage. In special subacute hepatic studies, oral doses of 125 mg/kg and higher in rats were associated with histological changes in the liver which were reversible when the drug was discontinued. In dogs, doses of 20 mg/kg were also associated with hepatic changes; however, these changes were reversible with continued dosing.

Dermatological events (see ADVERSE REACTIONS section) may be transient and may disappear despite continued use of CARDIZEM. However, skin eruptions progressing to erythema multiforme and/or exfoliative dermatitis have also been infrequently reported. Should a dermatologic reaction persist, the drug should be discontinued.

Drug Interaction. Due to the potential for additive effects, caution and careful titration are warranted in patients receiving CARDIZEM concomitantly with any agents known to affect cardiac contractility and/or conduction. (See WARNINGS.) Pharmacologic studies indicate that there may be additive effects in prolonging AV conduction when using beta-blockers or digitalis concomitantly with CARDIZEM. (See WARNINGS.)

As with all drugs, care should be exercised when treating patients with multiple medications. CARDIZEM undergoes biotransformation by cytochrome P-450 mixed function oxidase. Coadministration of CARDIZEM with other agents which follow the same route of biotransformation may result in the competitive inhibition of metabolism. Dosages of similarly metabolized drugs such as cyclosporin, particularly those of low therapeutic ratio or in patients with renal and/or hepatic impairment, may require adjustment when starting or stopping concomitantly administered CARDIZEM to maintain optimum therapeutic blood levels.

Beta-blockers: Controlled and uncontrolled domestic studies suggest that concomitant use of CARDIZEM and beta-blockers is usually well tolerated, but available data are not sufficient to predict the effects of concomitant treatment in patients with left ventricular dysfunction or cardiac conduction abnormalities.

Administration of CARDIZEM (diltiazem hydrochloride) concomitantly with propranolol in five normal volunteers resulted in increased propranolol levels in all subjects and bioavailability of propranolol was increased approximately 50%. If combination therapy is initiated or withdrawn in conjunction with propranolol, an adjustment in the propranolol dose may be warranted. (See WARNINGS.)

Cimetidine: A study in six healthy volunteers has shown a significant increase in peak diltiazem plasma levels (58%) and area-under-the-curve (53%) after a 1-week course of cimetidine at 1,200 mg per day and diltiazem 60 mg per day. Ranitidine produced smaller, nonsignificant increases. The effect may be mediated by cimetidine's known inhibition of hepatic cytochrome P-450, the enzyme system probably responsible for the first-pass metabolism of diltiazem. Patients currently receiving diltiazem therapy should be carefully monitored for a change in pharmacological effect when initiating and discontinuing therapy with cimetidine. An adjustment in the diltiazem dose may be warranted.

Digitalis: Administration of CARDIZEM with digoxin in 24 healthy male subjects increased plasma digoxin concentrations approximately 20%. Another investigator found no increase in digoxin levels in 12 patients with coronary artery disease. Since there have been conflicting results regarding the effect of digoxin levels, it is recommended that digoxin levels be monitored when initiating, adjusting, and discontinuing CARDIZEM therapy to avoid possible over- or under-digitalization. (See WARNINGS.)

Anesthetics: The depression of cardiac contractility, conductivity, and automaticity as well as the vascular dilation associated with anesthetics may be potentiated by calcium channel blockers. When used concomitantly, anesthetics and calcium blockers should be titrated carefully.

Carcinogenesis, Mutagenesis, Impairment of Fertility. A 24-month study in rats at oral dosage levels of up to 100 mg/kg/day, and a 21-month study in mice at oral dosage levels of up to 30 mg/kg/day showed no evidence of carcinogenicity. There was also no mutagenic response in vitro or in vivo in mammalian cell assays or in vitro in bacteria. No evidence of impaired fertility was observed in a study performed in male and female rats at oral dosages of up to 100 mg/kg/day.

Pregnancy. Category C. Reproduction studies have been conducted in mice, rats, and rabbits. Administration of doses ranging from five to ten times greater (on a mg/kg basis) than the daily recommended therapeutic dose has resulted in embryo and fetal lethality. These doses, in some studies, have been reported to cause skeletal abnormalities. In the perinatal/postnatal studies, there was an increased incidence of stillbirths at doses of 20 times the human dose or greater.

There are no well-controlled studies in pregnant women; therefore, use CARDIZEM in pregnant women only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers. Diltiazem is excreted in human milk. One report suggests that concentrations in breast milk may approximate serum levels. If use of CARDIZEM is deemed essential, an alternative method of infant feeding should be instituted.

Pediatric Use. Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Serious adverse reactions have been rare in studies carried out to date, but it should be recognized that patients with impaired ventricular function and cardiac conduction abnormalities have usually been excluded from these studies.

The adverse events described below represent events observed in clinical studies of hypertensive patients receiving either CARDIZEM Tablets or CARDIZEM SR Capsules as well as experiences observed in studies of angina and during marketing. The most common events in hypertension studies are shown in a table with rates in placebo patients shown for comparison. Less common events are listed by body system; these include any adverse reactions seen in angina studies that were not observed in hypertension studies. In all hypertensive patients taking CARDIZEM Tablets or CARDIZEM SR Capsules studied (over 900), the most common adverse events were edema (9%), headache (8%), dizziness (6%), asthenia (5%), sinus bradycardia (3%), flushing (3%), and first-degree AV block (3%). Only edema and perhaps bradycardia and dizziness were dose related.

DOUBLE BLIND PLACEBO CONTROLLED HYPERTENSION TRIALS

ADVERSE	DILTIAZEM N=315 # PTS (%)	PLACEBO N=211 # PTS (%)
Headache	38 (12%)	17 (8%)
AV Block First Degree	24 (7.6%)	4 (1.9%)
Dizziness	22 (7%)	6 (2.8%)
Edema	19 (6%)	2 (0.9%)
Bradycardia	19 (6%)	3 (1.4%)
ECG Abnormality	13 (4.1%)	3 (1.4%)
Asthenia	10 (3.2%)	1 (0.5%)
Constipation	5 (1.6%)	2 (0.9%)
Dyspepsia	4 (1.3%)	1 (0.5%)
Nausea	4 (1.3%)	2 (0.9%)
Palpitations	4 (1.3%)	2 (0.9%)
Polyuria	4 (1.3%)	2 (0.9%)
Somnolence	4 (1.3%)	—
Alk Phos Increase	3 (1%)	1 (0.5%)
Hypotension	3 (1%)	1 (0.5%)
Insomnia	3 (1%)	1 (0.5%)
Rash	3 (1%)	1 (0.5%)
AV Block Second Degree	2 (0.6%)	—

The following table presents the most common adverse reactions reported i placebo-controlled trials in patients receiving CARDIZEM CD up to 360 mg wit rates in placebo patients shown for comparison.

ADVERSE REACTION	CARDIZEM CD N=324	PLACEBO N=175
HEADACHE	9.0%	8.0%
BRADYCARDIA	4.3%	2.3%
EDEMA	3.7%	2.3%
DIZZINESS	3.1%	3.4%
ECG ABNORMALITY	3.1%	2.9%
AV BLOCK FIRST DEGREE	2.2%	—
ASTHENIA	1.9%	1.7%

In clinical trials of CARDIZEM CD Capsules, CARDIZEM Tablets, and CARDIZEM S Capsules involving over 3000 patients, the most common events (ie, greate than 1%) were edema (4.9%), headache (4.9%), dizziness (3.5%), asthenia (2.7%), first-degree AV block (2.2%), bradycardia (1.6%), flushing (1.5%), nausea (1.4%), rash (1.3%), and dyspepsia (1.2%).

In addition, the following events were reported infrequently (less than 1%).

Cardiovascular: Angina, arrhythmia, AV block (second- or third-degree), bundle branch block, congestive heart failure, ECG abnormalities, hypotension palpitations, syncope, tachycardia, ventricular extrasystoles.

Nervous System: Abnormal dreams, amnesia, depression, gait abnormality hallucinations, insomnia, nervousness, paresthesia, personality change somnolence, tinnitus, tremor.

Gastrointestinal: Anorexia, constipation, diarrhea, dry mouth, dysgeusia, milk elevations of SGOT, SGPT, LDH, and alkaline phosphatase (see hepati warnings), thirst, vomiting, weight increase.

Dermatological: Petechiae, photosensitivity, pruritus, urticaria.

Other: Amblyopia, CPK increase, dyspnea, epistaxis, eye irritation hyperglycemia, hyperuricemia, impotence, muscle cramps, nasa congestion, nocturia, osteoarticular pain, polyuria, sexual difficulties.

The following postmarketing events have been reported infrequently i patients receiving CARDIZEM: alopecia, erythema multiforme, exfoliative dermatitis, extrapyramidal symptoms, gingival hyperplasia, hemolytic anemia increased bleeding time, leukopenia, purpura, retinopathy, and thrombocytopenia. In addition, events such as myocardial infarction have been observed which are not readily distinguishable from the natural histor of the disease in these patients. A number of well-documented cases o generalized rash, characterized as leukocytoclastic vasculitis, have been reported. However, a definitive cause and effect relationship between these events and CARDIZEM therapy is yet to be established.

HOW SUPPLIED

CARDIZEM® CD (diltiazem hydrochloride) is available as capsules of 180 mg, 240 mg, and 300 mg in bottles of 30 and 90, and in UDIP® packages of 100.

CARDIZEM® SR (diltiazem hydrochloride) is available as sustained release capsules of 60 mg, 90 mg, and 120 mg in bottles of 100, and in UDIP® packages of 100.

CARDIZEM® CD Product Information as of October 1991
CARDIZEM® SR Product Information as of January 1991

References: 1. Data on file, Marion Merrell Dow Inc. 2. Cramer JA, Mattson RH Prevey ML, et al. *JAMA*. 1989;261(22):3273-3274.

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signal-averaged electrocardiogram in the X, Y and Z axes. DDD pacing reduces obstruction to left ventricular outflow and alters the depolarization and repolarization phases of the surface electrocardiogram, but the interrelation of these changes needs further elucidation.

657

Long-Term Follow-Up of Patients Undergoing Myotomy/Myectomy for Obstructive Hypertrophic Cardiomyopathy

Lawrence H. Cohn, Hemant Trehan, and John J. Collins, Jr.

Thirty-one patients with hypertrophic cardiomyopathy were followed up to 14 years after a radical myotomy/myectomy of the septum. Left ventricular subaortic obstruction was reduced significantly from a mean of 96 to 4.5 mm Hg measured 6.5 years postoperatively. Associated coronary artery disease carries with it a poor long-term prognosis.

CONGENITAL HEART DISEASE

661

1,000 Consecutive Children with a Cardiac Malformation with 26- to 37-Year Follow-Up

James H. Moller and Ray C. Anderson

The status of 997 of 1,000 consecutive children with a cardiac malformation was determined 26 to 37 years after initial cardiac evaluation. Two hundred eighty-five have died and 632 are in good or excellent status. The remaining 80 patients have cardiac symptoms and some of these are noncorrectable conditions. There have been 21 episodes of endocarditis, 5 patients with a brain abscess, and 5 with a malignancy. Currently 22 are receiving a cardiac medication.

668

Diagnosis of Patent Foramen Ovale by Transesophageal Echocardiography and Association with Cerebral and Peripheral Embolic Events

Dirk Hausmann, Andreas Mügge, Isolde Becht, and Werner G. Daniel

Patent foramen ovale (PFO) was detected in 50 of 238 patients (21%) by transesophageal (TEE) contrast echocardiography compared with 45 patients (19%) by color Doppler TEE (p = not significant). In 198 patients in whom transthoracic (TTE) and TEE contrast studies could be compared, PFO was found in 15 patients (8%) by TTE and in 44 patients (22%) by TEE ($p < 0.001$). A PFO could be seen in 9 of 18 patients (50%) aged <40 years with otherwise unexplained ischemic stroke. This prevalence was significantly higher than in patients with arterial embolism explained by other cardiac abnormalities (21% with PFO) and in patients without embolic events (21% with PFO). It is concluded that contrast or color Doppler TEE is the method of choice for diagnosing PFO.

MISCELLANEOUS

673
Hyperventilation Syndrome and the Assessment of Treatment for Functional Cardiac Symptoms
Steven DeGuire, Richard Gevirtz, Yoshito Kawahara, and William Maguire

Three types of breathing retraining were compared with a no-treatment control group to evaluate the effectiveness of breathing retraining on reducing functional cardiac symptoms for patients with signs of hyperventilation syndrome. Although no specific type of breathing retraining studied emerged as being more advantageous, results support the efficacy of breathing retraining in reducing cardiac symptoms. Patients with mitral valve prolapse syndrome were included in the study and responded to breathing retraining as well as did those without mitral valve prolapse.

678
Percutaneous Pericardial Catheter Drainage in Childhood
Evan M. Zahn, Christine Houde, Lee Benson, and Robert M. Freedom

The technique and clinical course of 41 consecutive pediatric patients (mean age 7.6 ± 5.8 years) who underwent percutaneous pericardial drain placement were reviewed. Indications for drainage included increasing effusion size (48%), clinical deterioration (33%), echocardiographic evidence of hemodynamic compromise (12%) and cardiac tamponade (7%). Insertion was successful in all but 1 patient (98%) and successful evacuation of the pericardial space was achieved in 93% (38 of 41) of patients. There was 1 death (<2 years of age) and 4 minor complications, 3 of which occurred in patients <2 years of age. There were 3 instances (7%) of drainage catheter occlusion necessitating surgical creation of a pericardial window. It is concluded that placement of a percutaneous pericardial catheter is safe and effective in providing definitive drainage of the pericardial space in the pediatric age group. Children younger than age 2 years may be at increased risk for complications.

681
A New Classification of Left Ventricular Geometry in Patients with Cardiac Disease Based on M-Mode Echocardiography
Farhad U. Huwez, Stuart D. Pringle, and Peter W. Macfarlane

M-mode echocardiograms of 202 cardiac patients were studied with respect to the pattern of left ventricular (LV) geometry. Patients with normal LV mass and volume were separated from those who had LV hypertrophy or enlargement on the basis of LV mass and volume indexed to body surface area. The relative wall thickness that is currently used to classify LV hypertrophy/enlargement was found to be inadequate for differentiating between concentric and eccentric types of LV hypertrophy. A new M-mode echocardiographic classification is therefore proposed that accurately separates the different types of LV enlargement; it also allows identification of patients who have chronically dilated left ventricles at the expense of thin walls and thus have normal LV mass.

Continued on page A43

INTRODUCING NEW Ismo™ 20 mg tablets

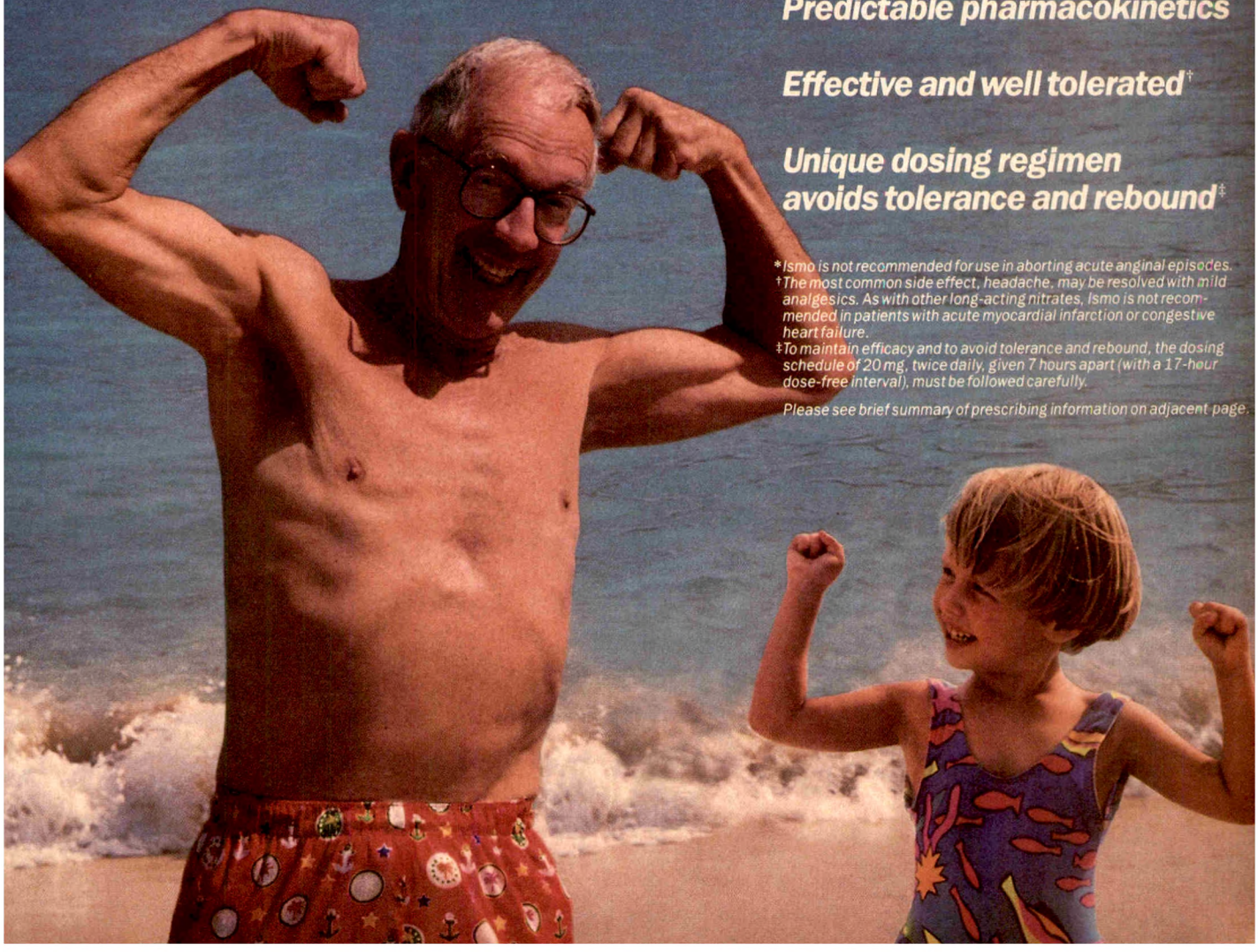
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Unique dosing regimen avoids tolerance and rebound‡



*Ismo is not recommended for use in aborting acute anginal episodes.

†The most common side effect, headache, may be resolved with mild analgesics. As with other long-acting nitrates, Ismo is not recommended in patients with acute myocardial infarction or congestive heart failure.

‡To maintain efficacy and to avoid tolerance and rebound, the dosing schedule of 20 mg, twice daily, given 7 hours apart (with a 17-hour dose-free interval), must be followed carefully.

Please see brief summary of prescribing information on adjacent page.

Ismo® (isosorbide mononitrate) 20 mg tablets

BRIEF SUMMARY (*FOR FULL PRESCRIBING INFORMATION AND PATIENT INFORMATION, SEE PACKAGE CIRCULAR.*)

Indications and Usage Ismo is indicated for prevention of angina pectoris due to coronary artery disease. The onset of action is not rapid enough for it to be useful in aborting an acute anginal episode.

Clinical Pharmacology Isosorbide mononitrate is the major active metabolite of isosorbide dinitrate; most of the clinical activity of the dinitrate comes from the mononitrate. Ismo is not subject to first-pass metabolism in the liver and the absolute bioavailability of isosorbide mononitrate from Ismo tablets is nearly 100%. The rate of clearance of Ismo is the same in healthy young adults, in patients with various degrees of renal, hepatic, or cardiac dysfunction, and in the elderly.

Several well-controlled studies have demonstrated that active nitrates were indistinguishable from placebo after 24 hours (or less) of continuous therapy due to the development of tolerance. Only after nitrates are absent from the body for several hours is their antianginal efficacy restored.

The drug-free interval sufficient to avoid tolerance to isosorbide mononitrate is not completely defined. The only regimen shown to avoid development of tolerance with isosorbide mononitrate involves two daily doses of Ismo tablets given 7 hours apart, so there is a gap of 17 hours between the second dose of each day and the first dose of the next day. Taking account of the relatively long half-life of isosorbide mononitrate this result is consistent with those obtained for other organic nitrates.

The same twice-daily regimen of Ismo tablets successfully avoided significant rebound/withdrawal effects. In studies of other nitrates, the incidence and magnitude of such phenomena appear to be highly dependent upon the schedule of nitrate administration.

Contraindications Allergic reactions are extremely rare, but do occur. Ismo is contraindicated in patients allergic to it.

Warnings Because the effects of Ismo are difficult to terminate rapidly and have not been established in patients with acute myocardial infarction (MI) or congestive heart failure (CHF), this drug is not recommended in these patients. If Ismo is used in these patients, careful clinical or hemodynamic monitoring is required to avoid the hazards of hypotension and tachycardia.

Precautions GENERAL Severe hypotension, particularly with upright posture, may occur with even small doses. Therefore, use with caution in patients who may be volume depleted or who are already hypotensive. Paradoxical bradycardia and increased angina pectoris may accompany Ismo-induced hypotension.

Nitrates may aggravate angina caused by hypertrophic cardiomyopathy.

INFORMATION FOR PATIENTS Tell patients they must carefully follow the prescribed dosing schedule (2 doses taken 7 hours apart) to maintain the antianginal effect (eg, take first dose on awakening and second dose 7 hours later).

Daily headaches sometimes accompany treatment with nitrates, including Ismo, and are a marker of drug activity. Patients with headaches should not alter their treatment schedule since loss of headache may be associated with simultaneous loss of antianginal efficacy. Headaches may be treated with aspirin and/or acetaminophen without affecting the antianginal activity of Ismo.

Light-headedness on standing, especially just after rising from a recumbent or seated position, may occur. This may be more frequent in patients who have consumed alcohol.

DRUG INTERACTIONS Vasodilating effects of Ismo may be additive with those of other vasodilators, especially alcohol.

Marked symptomatic orthostatic hypotension has been reported when calcium channel blockers and organic nitrates were used in combination. Dose adjustments of either class of agents may be necessary.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY No carcinogenic effects were observed in mice or rats exposed to oral Ismo, nor were adverse effects on rat fertility observed.

No mutagenic activity was seen in *in vitro* or *in vivo* assays.

PREGNANCY CATEGORY C Ismo has been shown to have embryocidal effects in rats and rabbits at doses at least 70 times the maximum human dose. There are no adequate and well-controlled studies in pregnant women. Use during pregnancy only if potential benefit justifies potential fetal risk.

NURSING MOTHERS Excretion in human milk is unknown. Use caution if administered to a nursing woman.

PEDIATRIC USE Safety and effectiveness have not been established.

Adverse Reactions Frequency of Adverse Reactions (Discontinuations)* Occurring in >1% of Subjects

	6 Controlled U.S. Studies		92 Clinical Studies
Dose	Placebo	20 mg	(varied)
Patients	204	219	3344
Headache	9% (0%)	38% (9%)	19% (4.3%)
Dizziness	1% (0%)	5% (1%)	3% (0.2%)
Nausea, Vomiting	<1% (0%)	4% (3%)	2% (0.2%)

*Some individuals discontinued for multiple reasons

Fewer than 1% of patients reported each of the following (in many cases a causal relationship is uncertain): *Cardiovascular;* angina pectoris, arrhythmias, atrial fibrillation, hypotension, palpitations, postural hypotension, premature ventricular contractions, supraventricular tachycardia, syncope. *Dermatologic;* pruritus, rash. *Gastrointestinal;* abdominal pain, diarrhea, dyspepsia, tenesmus, tooth disorder, vomiting. *Genitourinary;* dysuria, impotence, urinary frequency. *Miscellaneous;* asthenia, blurred vision, cold sweat, diplopia, edema, malaise, neck stiffness, rigors. *Musculoskeletal;* arthralgia. *Neurologic;* agitation, anxiety, confusion, dyscoordination, hypoesthesia, hypokinesia, increased appetite, insomnia, nervousness, nightmares. *Respiratory;* bronchitis, pneumonia, upper respiratory tract infection.

Rarely, ordinary doses of organic nitrates have caused methemoglobinemia in normal-seeming patients (See **Overdosage).**

Overdosage The ill effects of overdosage are generally related to the ability of Ismo to induce vasodilation, venous pooling, reduced cardiac output and hypotension. Symptoms may include increased intracranial pressure, with any or all of persistent throbbing headache, confusion, and moderate fever; vertigo; palpitations; visual disturbances; nausea and vomiting (possibly with colic and even bloody diarrhea); syncope (especially with upright posture); air hunger and dyspnea, later followed by reduced ventilatory effort; diaphoresis, with the skin either flushed or cold and clammy; heart block and bradycardia; paralysis; coma; seizures and death.

Serum levels have no role in managing overdose. The likely lethal dose in humans is unknown.

There is neither a specific antidote to Ismo overdose, nor data to suggest a means for accelerating its elimination from the body; dialysis is ineffective. Hypotension associated with Ismo overdose results from venodilatation and arterial hypovolemia; therefore, direct therapy toward an increase in central fluid volume. Use of arterial vasoconstrictors (eg, epinephrine) is likely to do more harm than good. In patients with renal disease or CHF, treatment of Ismo overdose may be difficult and require invasive monitoring.

Methemoglobinemia has occurred in patients receiving other organic nitrates, and probably could occur as a side effect of Ismo. There are case reports of significant methemoglobinemia in association with moderate overdoses of organic nitrates. None of the affected patients had been thought to be unusually susceptible. Suspect the diagnosis in patients who exhibit signs of impaired oxygen delivery despite adequate cardiac output and adequate arterial pO_2. Classically, methemoglobinemic blood is chocolate brown, without color change on exposure to air. The treatment of choice for methemoglobinemia is methylene blue, 1-2 mg/kg intravenously.

DOSAGE AND ADMINISTRATION The recommended regimen of Ismo tablets is 20 mg (one tablet) twice daily, with the two doses given 7 hours apart. For most patients, this can be accomplished by taking the first dose on awakening and the second dose 7 hours later. This dosing regimen provides a daily nitrate-free interval to avoid the development of refractory tolerance (see **Clinical Pharmacology).**

Well-controlled studies have shown that tolerance to Ismo tablets is avoided when using the twice daily regimen in which the two doses are given 7 hours apart. This regimen has been shown to have antianginal efficacy beginning 1 hour after the first dose and lasting at least 5 hours after the second dose. The duration (if any) of antianginal activity beyond 12 hours has not been studied; large controlled studies with other nitrates suggest that no dosing regimen should be expected to provide more than 12 hours of continuous antianginal efficacy per day.

Dosage adjustments are not necessary in the elderly patients or in patients with altered renal or hepatic function.

This Brief Summary is based upon the current Ismo direction circular, CI 4127-1, Issued January 10, 1992.

A·H·ROBINS

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Effectively controls hypertension with no adverse effect on lipids[3-6]



The fastest growing brand of diuretic when used in combination with ACE inhibitors or calcium antagonists*

*Scott-Levin Associates, Inc., *Physician Drug and Diagnosis Audit (PDDA)*, January 1991--December 1991.

Please see brief summary of prescribing information below.

compatible ONCE A DAY

LOZOL® INDAPAMIDE 2.5mg TABLET

LOZOL® (indapamide) **2.5 mg tablets**
BRIEF SUMMARY

INDICATIONS AND USAGE: LOZOL (indapamide) is indicated for the treatment of hypertension, alone or in combination with other antihypertensive drugs, and for the treatment of salt and fluid retention associated with congestive heart failure.
Usage in Pregnancy: See PRECAUTIONS.

CONTRAINDICATIONS: Anuria, hypersensitivity to indapamide or other sulfonamide-derived drugs.

WARNINGS: Infrequent cases of severe hyponatremia, accompanied by hypokalemia, have been reported with the use of recommended doses of indapamide primarily in elderly females. Symptoms were reversed by electrolyte replenishment (see PRECAUTIONS). Hypokalemia occurs commonly with diuretics (**see ADVERSE REACTIONS, hypokalemia**), and electrolyte monitoring is essential. In general, diuretics should not be given with lithium.

PRECAUTIONS: Perform serum electrolyte determinations at appropriate intervals, especially in patients who are vomiting excessively or receiving parenteral fluids, in patients subject to electrolyte imbalance, or in patients on a salt-restricted diet. In addition, patients should be observed for clinical signs of fluid or electrolyte imbalance, such as hyponatremia, hypochloremic alkalosis, or hypokalemia. The risk of hypokalemia secondary to diuresis and natriuresis is increased with larger doses, with brisk diuresis, with severe cirrhosis, and with concomitant use of corticosteroids or ACTH. Interference with adequate oral intake of electrolytes will also contribute to hypokalemia. Hypokalemia can sensitize or exaggerate the response of the heart to the toxic effects of digitalis, such as increased ventricular irritability.
Dilutional hyponatremia may occur in edematous patients; appropriate treatment is usually water restriction. In actual salt depletion, appropriate replacement is the treatment of choice. Chloride deficit is usually mild, not requiring specific treatment except in extraordinary circumstances (liver, renal disease).
Hyperuricemia may occur, and frank gout may be precipitated in certain patients receiving indapamide. Serum concentrations of uric acid should be monitored periodically.
Use with caution in patients with severe renal disease; consider withholding or discontinuing if progressive renal impairment is observed. Renal function tests should be performed periodically.
Use with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma.
Latent diabetes may become manifest and insulin requirements in diabetic patients may be altered during thiazide administration. Serum concentrations of glucose should be monitored routinely during treatment with indapamide.
Calcium excretion is decreased by diuretics pharmacologically related to indapamide. Serum concentrations of calcium increased only slightly with indapamide in long-term studies of hypertensive patients. Indapamide may decrease serum PBI levels without signs of thyroid disturbance. Complications of hyperparathyroidism have not been seen. Discontinue before tests of parathyroid function are performed.
Thiazides have exacerbated or activated systemic lupus erythematosus. Consider this possibility with indapamide.

DRUG INTERACTIONS: LOZOL may add to or potentiate the action of other antihypertensive drugs. The antihypertensive effect of the drug may be enhanced in the postsympathectomized patient. Indapamide may decrease arterial responsiveness to norepinephrine, but this does not preclude the use of norepinephrine.
In mouse and rat lifetime carcinogenicity studies, there were no significant differences in the incidence of tumors between the indapamide-treated animals and the control groups.

Pregnancy Category B: Diuretics cross the placental barrier and appear in cord blood. Indapamide should be used during pregnancy only if clearly needed. Use may be associated with fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse effects that have occurred in adults. It is not known whether this drug is excreted in human milk. If use of this drug is deemed essential, the patient should stop nursing.

ADVERSE REACTIONS: Most adverse effects have been mild and transient. From Phase II placebo-controlled studies and long-term controlled clinical trials, adverse reactions with ≥ 5% cumulative incidence: headache, dizziness, fatigue, weakness, loss of energy, lethargy, tiredness or malaise, muscle cramps or spasm or numbness of the extremities, nervousness, tension, anxiety, irritability or agitation; < 5% cumulative incidence: lightheadedness, drowsiness, vertigo, insomnia, depression, blurred vision, constipation, nausea, vomiting, diarrhea, gastric irritation, abdominal pain or cramps, anorexia, orthostatic hypotension, premature ventricular contractions, irregular heart beat, palpitations, frequency of urination, nocturia, polyuria, rash, hives, pruritus, vasculitis, impotence or reduced libido, rhinorrhea, flushing, hyperuricemia, hyperglycemia, hyponatremia, hypochloremia, increase in serum BUN or creatinine, glycosuria, weight loss, dry mouth, tingling of extremities. Hypokalemia with concomitant clinical signs or symptoms occurred in 3% of patients receiving indapamide 2.5 mg q.d. and 7% of patients receiving indapamide 5 mg q.d. In long-term controlled clinical trials comparing the hypokalemic effects of daily doses of indapamide and hydrochlorothiazide, however, 47% of patients receiving indapamide 2.5 mg, 72% of patients receiving indapamide 5 mg, and 44% of patients receiving hydrochlorothiazide 50 mg had at least one potassium value (out of a total 11 taken during the study) below 3.5 mEq/L. On the indapamide 2.5 mg group, over 50% of those patients returned to normal serum potassium values without intervention. Other adverse reactions reported with antihypertensive/diuretics are intrahepatic cholestatic jaundice, sialadenitis, xanthopsia, photosensitivity, purpura, bullous eruptions, Stevens-Johnson syndrome, necrotizing angiitis, fever, respiratory distress (including pneumonitis), anaphylactic reactions, agranulocytosis, leukopenia, thrombocytopenia, aplastic anemia.

CAUTION: Federal (U.S.A.) law prohibits dispensing without prescription.
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CORONARY ARTERY DISEASE

The American Journal of Cardiology

SEPTEMBER 1, 1992, VOL. 70, NO. 6

Performance Status and Outcome After Coronary Artery Bypass Grafting in Persons Aged 80 to 93 Years

Donald D. Glower, MD, Thomas D. Christopher, MD, Carmelo A. Milano, MD, William D. White, MPH, L. Richard Smith, PhD, Robert H. Jones, MD, and David C. Sabiston, Jr., MD

Although coronary artery bypass grafting (CABG) effectively eliminates or diminishes symptoms of myocardial ischemia, the overall performance status and functional outcome in elderly patients undergoing CABG is poorly documented. Therefore, 86 consecutive patients aged 80 to 93 years undergoing isolated CABG were reviewed. Preoperative, intraoperative, and postoperative characteristics and pre- and postoperative performance status (Karnofsky score) were examined. Forty patients (47%) were women, and most patients had highly symptomatic coronary artery disease with class III or IV angina in 94% and unstable angina in 90%. Significant co-morbid disease was present in 49% of patients, and cardiac catheterization revealed left main or 3-vessel disease in 74% of patients. The rate of significant in-hospital complications was 29%, with infection in 14%, stroke in 9%, and respiratory failure in 8% being most frequent. Median performance status (Karnofsky score) improved from 20 to 70% ($p = 0.0001$) with 89% of hospital survivors being discharged home. Factors associated with failure to achieve a successful functional outcome at discharge were presence of 1 or more preoperative co-morbid conditions ($p = 0.048$), preoperative myocardial infarction within 7 days of operation ($p < 0.01$), and postoperative low cardiac output ($p < 0.01$). Survival at 30 days, 6 months, and 3 years were 90, 78, and 64%, respectively. These data demonstrate that CABG can be offered to selected elderly patients with acceptable morbidity and mortality, marked improvement in performance status, and an acceptable quality of life.

(Am J Cardiol 1992;70:567–571)

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Many reports have established that, relative to younger patients, elderly patients aged >65 to 75 years are at increased risk for mortality and perioperative complications after coronary artery bypass grafting (CABG).[1,2] As the patient population with coronary artery disease grows older, and as morbidity and mortality with CABG continue to decrease, CABG in patients aged ≥80 years is now becoming quite common. Recent reports document increased but acceptable operative and long-term mortality rates after coronary bypass grafting in carefully selected patients over the age of 80, despite a significantly increased complication rate.[2–5] What remains to be documented is the overall performance status and functional outcome of these patients, many of whom have significant disability before operation. This latter issue is of increasing importance given recent concerns about the cost effectiveness of health care and about increasing limitations on the availability of health care resources. A study was therefore undertaken to examine in detail the performance status and outcome of CABG in patients aged ≥80 years at a single institution.

METHODS

A retrospective analysis was undertaken in all 86 patients aged 80 to 93 years undergoing isolated CABG at a single institution through February 1991. Data were collected regarding preoperative cardiac and surgical history, preoperative co-morbid conditions, preoperative performance status, cardiac catheterization data, intraoperative data, postoperative in-hospital course, performance status at discharge, and long-term survival. Significant coronary artery disease was defined as >70% stenosis of 1 or more coronary arteries. Performance status was assessed using the Karnofsky scoring system[6] (Table I), and symptomatic status both for angina and congestive heart failure was rated using the classification of the Canadian Cardiovascular Society.[7] All operations were performed with moderate systemic hypothermia (28 to 32°C) and either bubble or membrane oxygenators. Crystalloid cardioplegia was used in all patients except 2 in whom the aorta was not occluded because of extensive aortic disease. Follow-up was com-

TABLE I Karnofsky Performance Status Scale[6]

Normal activity; able to work; no special care	100% normal activity; 90% minor symptoms; 80% moderate symptoms
At home; unable to work; can care for most personal needs	70% self-care, less than normal activity; 60% needs some help; 50% needs much help
Needs institutional care	40% disabled; 30% severely disabled requiring special care; 20% needs active support; 10% moribund; 0% dead

TABLE II Preoperative Co-Morbid Disorders

Disorders	No. (% total)
Systemic hypertension (> 140/90 mm Hg)	58 (67)
Cerebrovascular disease	23 (27)
Cigarette smoking in last 10 years	23 (27)
Peripheral vascular disease	20 (23)
Diabetes mellitus	12 (14)
Chronic lung disease	11 (13)
Pulmonary edema	8 (9)
Chronic atrial fibrillation	4 (5)
Renal insufficiency (Cr ≥ 2)	4 (5)
Malignancy	3 (3)
Aortic aneurysm	2 (2)

Cr = creatinine.

plete to 1990 in 76 of 86 patients (88%), and mean follow-up duration was 17 ± 17 months.

The chi-square test and Fisher's exact test were used where appropriate to make univariate comparisons, and survival was computed by the method of Kaplan and Meier. All data are presented as mean ± standard deviation unless otherwise stated.

RESULTS

The first patient aged >80 years to undergo CABG at this institution did so in 1983. Since that time, CABG in patients aged >80 years has become increasingly frequent (Figure 1), and at this institution in 1990, 2.2% (20 of 893) of all patients undergoing isolated CABG were aged ≥80 years. Thirty-nine patients (45%) were women (mean age 81 ± 2 years, range 80 to 93). Seventy-two patients (84%) had class IV angina, and 17 (20%) had class III or IV congestive heart failure. The anginal pattern was classified as unstable in 45 patients, postinfarction in 19, progressive in 13, and stable in 9. Twenty-three patients (27%) had had a myocardial infarction within the previous 30 days, and 46 patients (53%) were underwent operation directly from the coronary care unit or the cardiac catheterization laboratory because of unstable or postinfarction angina. Eight patients required a preoperative intraaortic balloon pump, 4 patients required preoperative intubation, and 4 patients were in cardiogenic shock preoperatively. Only 4 patients had undergone preoperative thrombolysis, 2 patients had undergone previous CABG, and only 6 patients had undergone previous coronary angioplasty.

Significant co-morbid disease (renal, pulmonary, cerebrovascular, peripheral vascular, hematologic or gastrointestinal) was present in 42 of 86 patients (49%) including 31 patients (36%) with other significant vascular disease (Table II). Only 23 patients (27%) had smoked cigarettes in the last 10 years, and only 12 patients (14%) had diabetes mellitus, making diabetes and smoking less prevalent than in the overall population undergoing CABG at this institution.

Using standard definitions of coronary atherosclerosis,[8] cardiac catheterization demonstrated left main coronary disease in 21 patients (24%), 3-vessel coronary disease in 60 (70%), 2-vessel disease in 17 (20%), and 1-vessel disease in 5 (6%). On a scale of 1+ to 4+, thirteen patients had ≥2+ mitral regurgitation, 1 patient had 2+ aortic regurgitation, and 4 patients had mild aortic stenosis. Preoperative ejection fraction was <50% in 37 patients (43%) (mean ejection fraction 52 ± 11%, range 24 to 74).

Each patient underwent a mean of 3.0 ± 0.9 bypass grafts. Forty-five patients (52%) underwent internal mammary artery grafting, including 37 with isolated left internal mammary, 1 with isolated right internal mammary, and 7 (8%) with bilateral internal mammary

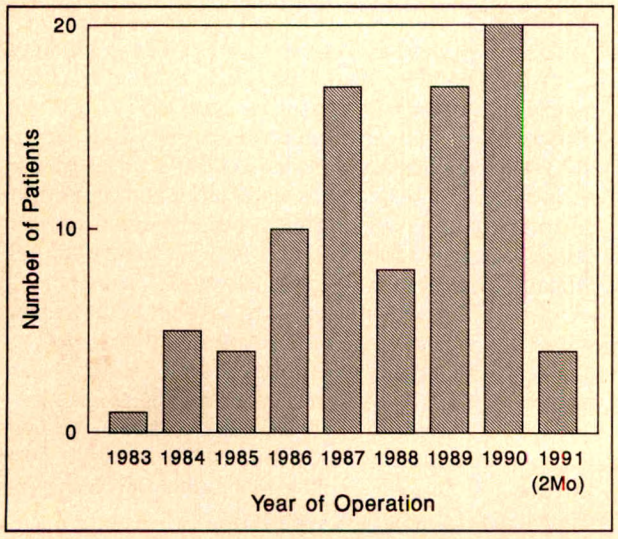


FIGURE 1. Frequency of isolated coronary artery bypass grafting in octogenarians over an 8-year period.

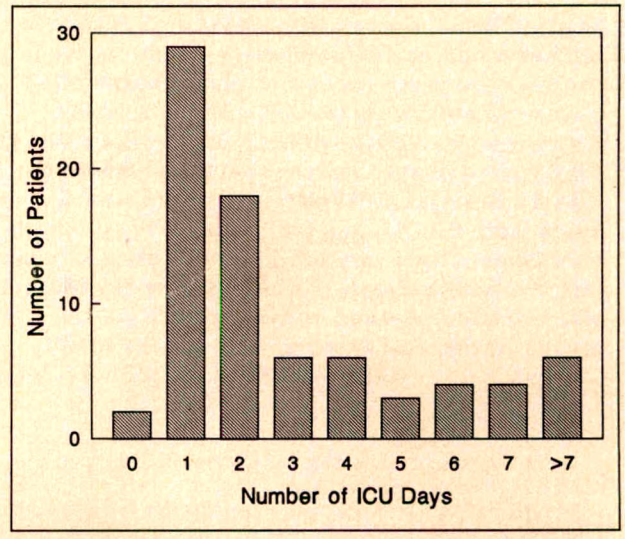


FIGURE 2. Duration of stay in the intensive care unit (ICU) after coronary bypass grafting in octogenarians.

artery grafting. Mean aortic clamp time was 45 ± 19 minutes with a cardiopulmonary bypass time of 111 ± 40 minutes.

Postoperatively, median stay in the intensive care unit was 2 days (25th and 75th percentiles were 1 and 4 days, respectively) (Figure 2). Significant postoperative complications occurred in 25 patients (29%), with stroke (8 patients), pneumonia (6 patients), other infection (11 patients), respiratory insufficiency (7 patients), bleeding (6 patients), and renal failure (4 patients) being most frequent. No patient developed mediastinitis. Twenty-eight patients (33%) required some form of postoperative organ support, including ≥2 inotropic agents in 18 patients (21%), nutritional support in 15 (17%), intraaortic balloon pumping in 13 (15%), ventilation >48 hours in 13 (15%), and dialysis in 3 (3%). Thirty-day mortality was 10.5% (9 of 86), with in-hospital mortality being 13.9% (12 of 86). The most frequent cause of in-hospital death was respiratory failure, occurring in 5 patients. Median hospital stay was 16 days (25th and 75th percentiles were 12 and 22 days, respectively) (Figure 3), and median postoperative stay was 10 days.

Mean Karnofsky score was 27 ± 15% preoperatively (median 20%) and was significantly increased to 60 ± 27% (median 70%) at discharge ($p = 0.0001$) (Figure 4). The median change in Karnofsky score was +40% (Figure 5), and 89% of hospital survivors achieved ≥20% increase in Karnofsky performance score at discharge. Eighty-nine percent (66 of 74) hospital survivors were discharged home, and of the remaining 11% (8 of 74), 5 were discharged to nursing facilities because of inadequate functional recovery, and 3 went to a nursing facility only because of inadequate family support. Late survival ± 95% confidence limits was 78 ± 7% at 6

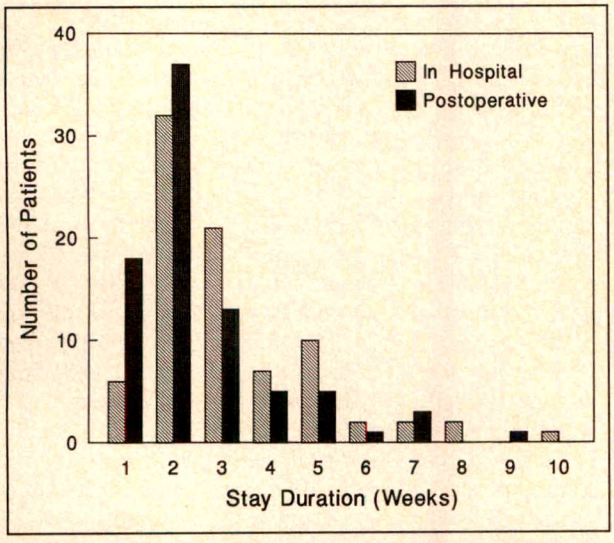


FIGURE 3. Duration of postoperative stay and hospital stay after coronary bypass grafting in octogenarians.

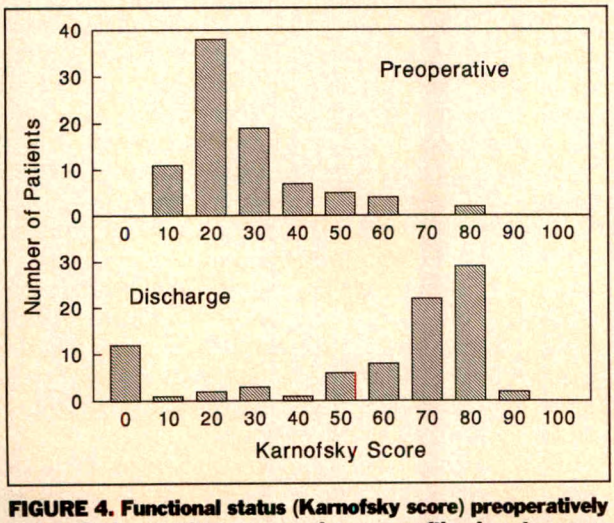


FIGURE 4. Functional status (Karnofsky score) preoperatively and at discharge after coronary bypass grafting in octogenarians.

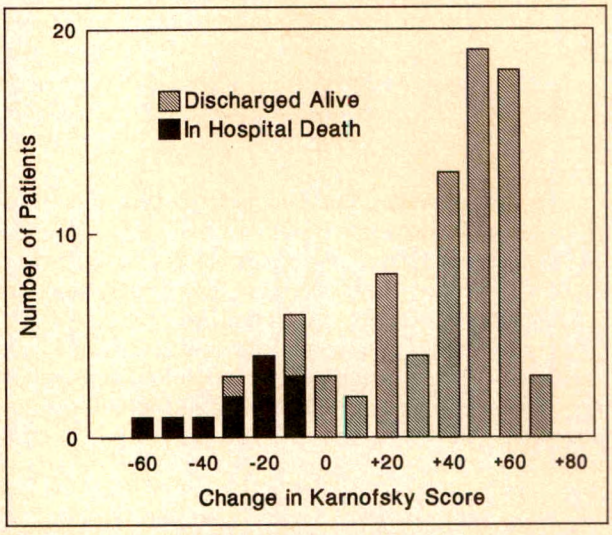


FIGURE 5. Change in Karnofsky functional status from preoperatively to time of discharge in octogenarians undergoing coronary bypass grafting.

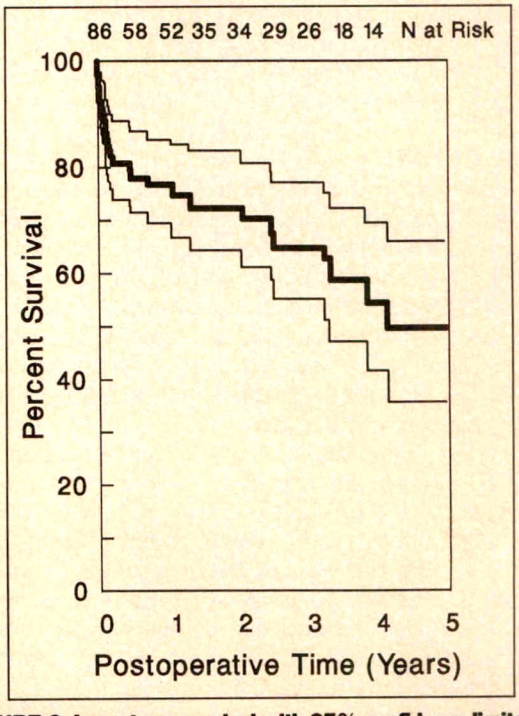


FIGURE 6. Long-term survival with 95% confidence limits after coronary bypass grafting in octogenarians.

months, 74 ± 9% at 1 year, 64 ± 11% at 3 years, and 50 ± 15% at 5 years (Figure 6). Cardiac causes were responsible for 56% (10 of 18) of late deaths.

Several preoperative, intraoperative and postoperative factors were associated with in-hospital mortality. The presence of ≥1 significant preoperative co-morbid disorder increased in-hospital mortality from 3 of 43 (7%) to 9 of 40 (23%) ($p = 0.04$). Preoperative myocardial infarction within 1 week of operation significantly increased in-hospital mortality from 7 of 74 (9%) to 6 of 12 (50%) ($p < 0.01$). Preoperative gender, congestive heart failure, ejection fraction, cardiogenic shock, year of operation, and internal mammary artery grafting were not significantly related to in-hospital mortality. Postoperative respiratory failure increased mortality from 4 of 64 (6%) to 8 of 18 (44%) ($p < 0.01$), postoperative low cardiac output (cardiac index <2.0 for 4 hours) increased mortality from 4 of 66 (6%) to 8 of 20 (40%) ($p < 0.01$), and postoperative stroke tended to increase in-hospital mortality from 7 of 78 (9%) to 3 of 8 (38%) ($p > 0.2$).

To examine the effects of perioperative factors on Karnofsky performance status at discharge, a successful functional outcome was defined as a discharge Karnofsky score of at least 60 and 20% greater than the preoperative score. By this definition, 60 of 86 (70%) patients achieved a successful functional outcome from coronary bypass grafting. One or more preoperative co-morbid conditions decreased the likelihood of a successful functional outcome from 29 of 36 (81%) to 29 of 48 (60%) ($p = 0.048$). Women tended to be more likely to have a successful functional outcome (32 of 40 or 80%) than men (28 of 46 or 61%) ($p = 0.054$), and women tended to have a lower hospital mortality rate (3 of 40 [8%] vs 9 of 46 [20%], $p = 0.10$). Preoperative myocardial infarction within 7 days of operation decreased the likelihood of successful functional outcome from 55 of 73 (75%) to 5 of 13 (38%) ($p < 0.01$). Postoperative low cardiac output decreased successful functional outcome from 52 of 66 (79%) to 8 of 20 (40%) ($p < 0.01$).

DISCUSSION

Few data are available regarding overall performance status and functional outcome after CABG in elderly patients. Data do exist regarding the New York Heart Association classification of cardiac symptoms after CABG, with the consensus indicating that CABG effectively relieves angina in most elderly patients.[3–5] In fact, Carey et al[9] found that at 5 to 10 years after CABG, symptomatic health status index for patients >65 years old was actually better than for younger patients. The major limitation of the New York Heart Association functional classification and other schemes such as health status index[9] is that they do not consider functional limitations not due to cardiac disease. In the extremely elderly, noncardiac disorders are common. Thus, an elderly patient who achieved an excellent cardiac functional outcome after coronary bypass grafting could still be very debilitated with poor quality of life and need for long-term nursing care.

The Karnofsky score was originally designed to assess overall performance status in cancer patients,[6] and Karnofsky performance status of patients after CABG has received little attention, perhaps because many patients have been quite functional both before and after surgery. On the other hand, elderly patients tend to have significant preoperative disability from noncardiac disease and thus might be expected to have impaired functional status both before and after CABG. As to our knowledge, this study is the first to document the overall performance status at the time of discharge after CABG in patients aged >80 years old. The percentage of patients discharged to a nursing home has not been previously documented in this population and is especially important in planning the future need for health care resources. This importance is heightened by the increasing numbers of elderly patients undergoing CABG, since operation may increase survival but also may increase the net number of patients requiring nursing care.

Elderly patients with coronary artery disease are a distinct population from younger patients in many ways. The lack of gender differences in the elderly, with 45% of patients in the present study being women as opposed to 23% of the general CABG population at this institution being women is noteworthy. Several studies reported that, as with younger patients, older women had a higher in-hospital mortality rate than their male counterparts.[2,4] Yet, other investigators found that female gender was an operative risk factor for young patients, but not for the elderly.[10] The present study demonstrated a trend for elderly women to have a decreased in-hospital mortality rate and improved functional outcome, but the trend did not achieve significance. In general, female gender appears to be a less significant risk factor in the elderly than in younger patients, and whether any effects of female gender in the elderly is in fact due to body weight or size remains unclear.

In addition to the lack of gender differences, elderly patients are more likely to have preoperative co-morbid conditions and perioperative complications than younger patients, as confirmed in this study and others.[2–5] The association between unfavorable outcome and such preoperative factors as recent myocardial infarction and 1 or more co-morbid disorders suggests that outcome in the elderly may be improved by careful patient selection. Unfortunately, older patients with highly symptomatic and severe coronary disease may actually have greater risk from nonoperative therapy than from operation, and selecting patients to improve operative mortality rate may not benefit the mortality rate in the population as a whole.[11] Moreover, the increased risk of patients undergoing operation early after myocardial infarction may reflect unstable myocardial perfusion requiring urgent intervention, and delay of operation may increase rather than decrease risk in these patients. Thus, preoperative risk factors such as co-morbid disease and recent infarction are useful in assessing prognosis, but the optimal role of risk factors in patient selection remains to be demonstrated.

The present study has several limitations. Although the small sample size decreases the ability to interrelate or detect factors influencing outcome, the present series is among the largest from any single institution to date.

Second, the fact that the 86 patients in this series are highly selected from the entire population of octogenarians does limit interpretation of this study. Third, the present study is a relatively short-term study since few patients ≥80 years old underwent CABG >5 to 7 years ago. Finally, the present study only begins to address optimal selection of elderly patients for CABG. Clearly, elderly patients with relatively few co-morbid conditions but with severely debilitating coronary artery disease may obtain excellent functional benefit from operation. Yet, further data are needed to address whether operating on elderly patients with even greater risk or less significant symptoms could also provide functional benefit at an acceptable cost. The role of alternative therapies such as angioplasty in the elderly similarly remains to be documented.

Despite the severe disability and frequent co-morbidity that characterized the preoperative octogenarians in the current study, the discharge performance status and the functional outcome were remarkably good. Seventy percent of patients experienced significant increase in overall performance status and were relatively self-sufficient at discharge. Only 18 patients (20%) either died before discharge or required nursing home placement for physical disability. Median stay in the intensive care unit (2 days) and postoperative in-hospital stay (10 days) were only slightly higher than those reported for the overall CABG population, and the cost of providing care to these patients would therefore be only modestly higher than average. Careful follow-up of these patients is required to continually reevaluate the benefit obtained given the increased cost of delivering health care in this high-risk group of patients.

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Exercise Echocardiography After Coronary Artery Bypass Grafting

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Exercise echocardiography was used to assess the adequacy of regional myocardial perfusion in 125 patients who had undergone coronary artery bypass grafting. There were 108 men and 17 women (mean age 65 years) evaluated from 6 weeks to 16 years (mean 7 years) after surgery. Resting parasternal long- and short-axis and apical 4- and 2-chamber echocardiograms were recorded, digitized and stored. Maximal, symptom-limited upright treadmill exercise was then performed with continuous electrocardiographic monitoring. Repeat echocardiographic imaging and digitization were repeated within 1 minute of exercise termination. Resting and postexercise digitized echocardiograms were compared. A normal regional wall motion response to exercise consisted of improved segmental contraction and was used to predict uncompromised regional vascular supply. Unimproved or worsened segmental contraction after exercise was abnormal and was used as a predictor of regional vascular insufficiency. All patients underwent cardiac catheterization within 1 month after exercise testing. Regional coronary insufficiency was considered to exist when a segment's major vascular conduit exhibited ≥50% luminal diameter reduction. Compared with the simultaneously acquired stress electrocardiogram, exercise echocardiography had superior sensitivity (98 vs 41%), specificity (92 vs 67%), positive predictive value (99 vs 91%), and negative predictive value (86 vs 12%) ($p < 0.001$, 0.1, 0.01 and < 0.001, respectively). In addition, exercise echocardiography correlated closely with the extent and regional distribution of compromised vascular supply. Exercise echocardiography is a highly sensitive, specific and accurate screening test for abnormal global and regional myocardial vascular supply in patients who have undergone coronary artery bypass grafting.

(Am J Cardiol 1992;70:572–576)

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Coronary artery bypass grafting is an effective, safe treatment for many patients with coronary artery disease. However, it has been well established that, over a period of time, bypass grafts, especially when constructed from autologous saphenous veins, may become stenosed or occluded, with a failure rate at 10 years that approaches 50%.[1–6] In addition, bypass patients are at risk for developing new arterial obstructions in postanastomotic vessels as well as in arteries that have little or no recognized disease at the time of surgery. The development of regional arterial insufficiency through graft failure or progressive native vessel disease may have serious consequences, including myocardial infarction, left ventricular dysfunction, arrhythmia and death. The identification of patients at risk for these sequelae may be the first step toward their prevention. Most screening tests for coronary insufficiency are designed to detect the consequences of provoked myocardial ischemia. Stress electrocardiography is of limited value as a screening test in bypass patients, because of the prevalence of numerous compounding influences on the electrocardiogram, such as medication, previous infarction and conduction abnormalities.[7–11] With the advent of computer technology, which makes possible the acquisition, digitization, storage and replay of echocardiographic images acquired from a single cardiac cycle, exercise echocardiography has emerged as a highly sensitive, specific and accurate screening test for coronary artery disease, which correlates closely with coronary angiography.[12–14] The purpose of this study was to evaluate exercise echocardiography as a noninvasive method for predicting the adequacy of regional myocardial perfusion in patients who have undergone coronary artery bypass grafting.

METHODS

Patients: The study population consisted of 125 patients seen in routine outpatient follow-up after bypass surgery, or because of symptoms, who underwent exercise echocardiography and subsequent cardiac catheterization. The decision to proceed with cardiac catheterization was made by the attending physician on clinical grounds, and the exercise electrocardiogram or echocardiogram, or both. There were 108 men and 17 women age range 40 to 80 years, mean 65). The interval between follow-up and surgery ranged between 6 weeks and 16½ years, averaging 6.7 years. At the time of evaluation, 74 patients had symptoms characterized as angina, 29 were asymptomatic, 12 had atypical chest pain and 10 had exertional dyspnea.

Echocardiography: Exercise echocardiography was performed according to the following protocol: Before

exercise, the patient was placed in the left lateral decubitus position. Parasternal long- and short-axis, and apical 2- and 4-chamber views were acquired, digitized and stored using a Hewlett-Packard 500K Echocardiograph and a Microsonics PreVue. Maximal, symptom-limited, upright treadmill exercise was then performed with electrocardiographic monitoring using a Bruce or modified Bruce protocol. At the termination of exercise, patients immediately resumed the left lateral decubitus position. Repeat imaging with digitization and storage of the standard views was completed within 1 minute of exercise termination. Rest and exercise images were then displayed side by side in a continuously replaying, cineloop format. No patient was excluded from analysis because of suboptimal or technically difficult echocardiographic studies.

Segmental regional wall motion analysis was performed as follows: A normal response, indicating normal segmental perfusion at rest and with exercise, consisted of improved wall motion regardless of resting contractile function. An abnormal response consisted of unimproved or deteriorated contractile function after exercise, interpreted to reflect provocation of regional myocardial ischemia. In patients with known previous transmural infarction, the infarct region was excluded from analysis if it was akinetic at rest and after exercise. If a segment that was akinetic at rest improved after exercise, even if it did not become hypercontractile, its vascular supply was predicted to be uncompromised. For the purpose of correlating with angiography, wall motion analysis was divided into anterior, posterolateral and inferior regions (Figure 1). Figure 2 depicts the schema according to which regional vascular compromise was predicted by abnormal exertional regional wall motion.

Cardiac catheterization: All 125 patients underwent subsequent cardiac catheterization with coronary artery and bypass graft angiography within 1 month after ex-

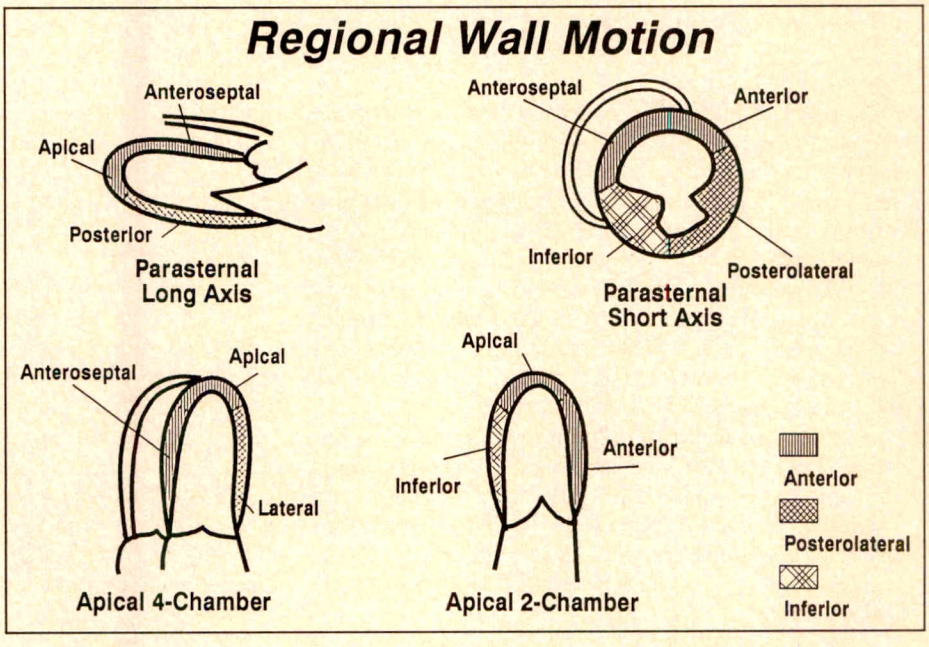


FIGURE 1. Schema according to which regional wall motion was evaluated.

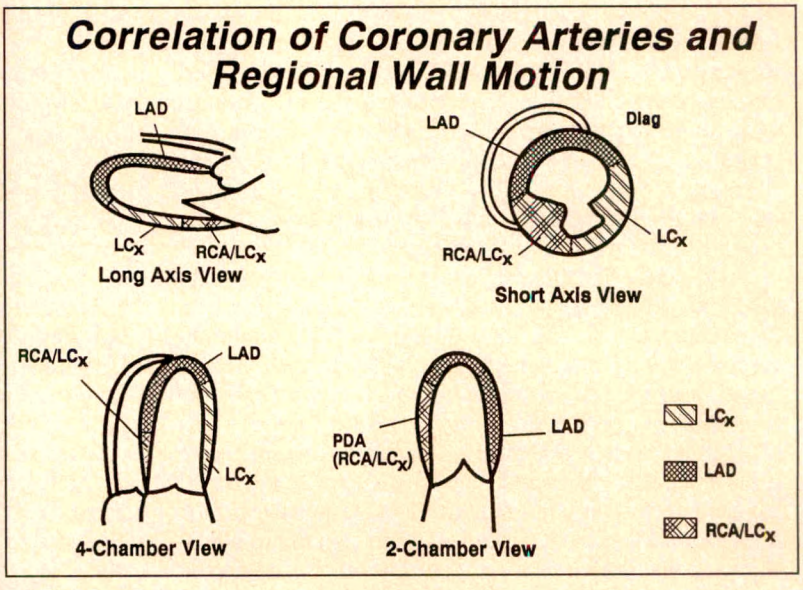


FIGURE 2. Schema according to which regional vascular compromise was predicted by abnormal exertional regional wall motion. Diag = diagonal; LAD = left anterior descending artery; LC_x = left circumflex artery; PDA = posterior descending artery; RCA = right coronary artery.

TABLE I Comparison of Exercise Echocardiography and Electrocardiography of Regional Myocardial Perfusion

Treadmill Marker	Sensitivity	95% Confidence Interval	Relative Risk Ratio*	p Value
Echo	98%	(96, 100)†	2.4	<0.001
ECG	41%	(32, 51)		
	Specificity			
Echo	92%	(78, 101)†	1.4	<0.11
ECG	67%	(40, 93)		
	Pos. Pred. Acc.			
Echo	99%	(97, 101)†	1.1	<0.01
ECG	91%	(83, 99)		
	Neg. Pred. Acc.			
Echo	86%	(67, 104)†	7.4	<0.0001
ECG	12%	(4, 19)		

*Relative risk ratio of the risk of erroneous detection or prediction using electrocardiography versus echocardiography.
†Upper limit is 1.00.
ECG = echocardiography; Echo = echocardiography; Neg. Pred. Acc. = negative predictive accuracy; Pos. Pred. Acc. = positive predictive accuracy.

ercise echocardiography. A myocardial region was considered to be significantly compromised if its major source of blood supply (native vessel or graft, or both) was reduced in diameter by ≥50%, based on our previous experience with patients who did not undergo revascularization.[15] Angiograms were interpreted by skilled angiographers who did not participate in exercise echocardiography interpretation. To correlate coronary anatomy with exercise echocardiography, regional vascular supply was divided into anterior, posterolateral and inferior zones.

The exercise electrocardiogram was scored as abnormal if there was ≥1 mm of horizontal or downsloping ST-segment depression 80 ms after the J point.

Statistical comparisons were made using the chi-square test. Differences were significant at $p < 0.05$.

RESULTS

Coronary arteriography demonstrated that 13 patients did not have significant coronary stenosis, as defined earlier. Twelve of these 13 patients had negative exercise echocardiograms, and 1 patient had an abnormal exercise echocardiogram. Each of the 112 patients with abnormal angiograms had at least 1 myocardial region for which the major vascular supply was narrowed by ≥50%. Of these 112 patients, 110 had abnormal exercise echocardiograms, but in 2 patients the exercise echocardiogram was normal.

As described earlier, regional vascular supply was divided into anterior, posterolateral and inferior zones. In 35 patients, a single region was found to have abnormal vascular supply by angiography. In 31 of these 35 patients the exercise echocardiogram correctly predicted single-region provokable ischemia, and it was the correct region in each patient. In 2 patients, 2 regions were predicted to be abnormal, one of which was abnormal by angiography in each patient. Two patients had normal exercise echocardiograms but had significant stenosis affecting the circumflex distribution. By angiography, 45 patients were found to have 2 regions with compromised vascular supply. In 39 of these, the exercise echocardiogram accurately forecast the number and location of these abnormal regions. In 3 patients the extent of abnormality was underestimated, and in 3 it was overestimated. In 32 patients, all 3 regions were abnormal by angiography. In 29 of these patients, exercise echocardiography accurately predicted this extent of vascular compromise. In 3 patients, exercise echocardiography predicted that the extent of ischemia was limited to 2 regions.

Exercise electrocardiography correlated poorly with angiography. Among patients who had fully adequate vascular supply, one-third had abnormal stress tests. Of patients with angiographic demonstration of vascular compromise of at least 1 region, the majority had normal exercise electrocardiograms. Nine patients were excluded from analysis because of left bundle branch block.

Table I compares the sensitivity, specificity and predictive accuracy of exercise echocardiography and exercise electrocardiography. Compared with exercise echocardiography, routine treadmill testing was insensitive, nonspecific and highly inaccurate in predicting the status of regional and global myocardial vascular supply.

Figures 3 and 4 are examples of abnormal exercise echocardiograms from our patient population.

DISCUSSION

Coronary artery bypass surgery has secured its role as a safe and effective treatment for severe coronary artery disease. However, 2 factors contribute to the eventual reappearance of myocardial ischemia in many patients. First, the failure rate of autologous saphenous vein grafts ranges between 10 and 20% by the end of the first postoperative year,[1,2,4] and this figure climbs to 50% after 10 years, with many of the remaining patent grafts showing signs of disease (atherosclerosis, intimal hyperplasia, ectasia and stenosis) after this interval.[5,6] Second, the frequently progressive behavior of native vessel atherosclerosis results in the development of new arterial stenoses in nonbypassed vessels as well as in the postanastomotic segments of bypassed arteries in many patients.

Digital exercise echocardiography has been shown to be a sensitive, specific and highly accurate predictor of the presence or absence of coronary artery disease in patients who have not undergone coronary revascularization procedures,[16–21] and the present report extends these findings to patients who have undergone CABG. Exercise echocardiography proved to be a highly accurate predictor of the status of regional vascular supply. In the small number of patients who were found at angiography to be free of vascular insufficiency, only 1 of 13 patients had a falsely positive test result. In patients with angiographic evidence of compromise perfusion, only 2 of 112 patients had falsely normal exercise echocardiograms. Moreover, there was a very close correlation between the ischemic zone detected by exercise echocardiography and myocardial segments perfused by stenosed arteries or grafts, or both, defined angiographically.

In contrast to the results of exercise echocardiography, exercise electrocardiography was a poor screening test for coronary/graft stenosis or occlusion in our patients. One-third of the patients without vascular compromise had abnormal stress electrocardiograms, and the majority of the patients with inadequate vascular supply had normal routine stress tests. In fact, the proportions of normal and abnormal exercise electrocardiograms were about the same in patients with and without jeopardized myocardium. Our findings in this regard are similar to those reported by others.[22]

Study limitations: Our patients do not represent a typical cross section of patients undergoing bypass surgery, but rather those who underwent outpatient evaluation and subsequent invasive study in the hospital. The decision to proceed with angiography was made on clinical grounds on the basis of symptoms or the results of exercise electrocardiography and echocardiography. This selection bias would be predicted to result in a high likelihood of vascular compromise in our patients, and this is reflected in the fact that 90% of our patients had abnormal angiograms. This high pretest likelihood of disease explains the exceptionally high positive predictive accuracy of exercise echo- and electrocardiography in our patients. However, this selection bias should also act to reduce the negative predictive accuracy. This effect is quite apparent for exercise electrocardiography, which had a negative predictive accuracy of only 16%. However, despite the high likelihood of disease in our patients, 87% of patients with negative exercise echocardiograms had negative angiograms. On the other hand, because sensitivity and specificity are determined in pre-

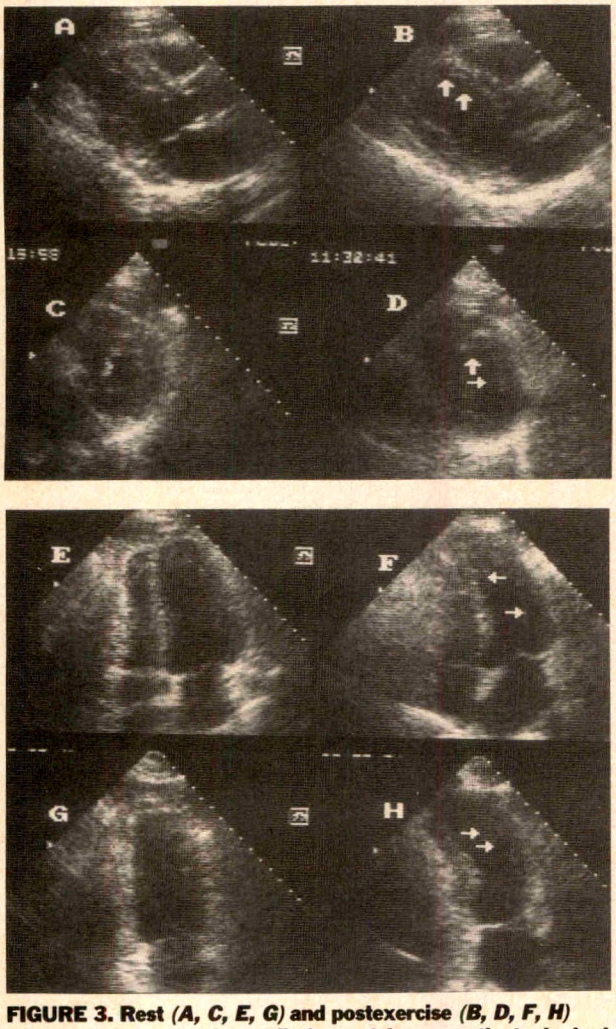


FIGURE 3. Rest *(A, C, E, G)* and postexercise *(B, D, F, H)* echocardiograms (end-systolic frames) from a patient who had undergone single saphenous vein bypass grafting of the left anterior descending coronary artery because of severe ostial left main stenosis 6 weeks before this stress test. Parasternal long- and short-axis views are shown in the *top 2 rows*, respectively; apical 4- and 2-chamber views are shown in *rows 3 and 4*. Although there were no symptoms and the stress electrocardiogram was normal, the anterior and lateral segments *(arrows)* became akinetic. Angiography confirmed total occlusion of the vein graft.

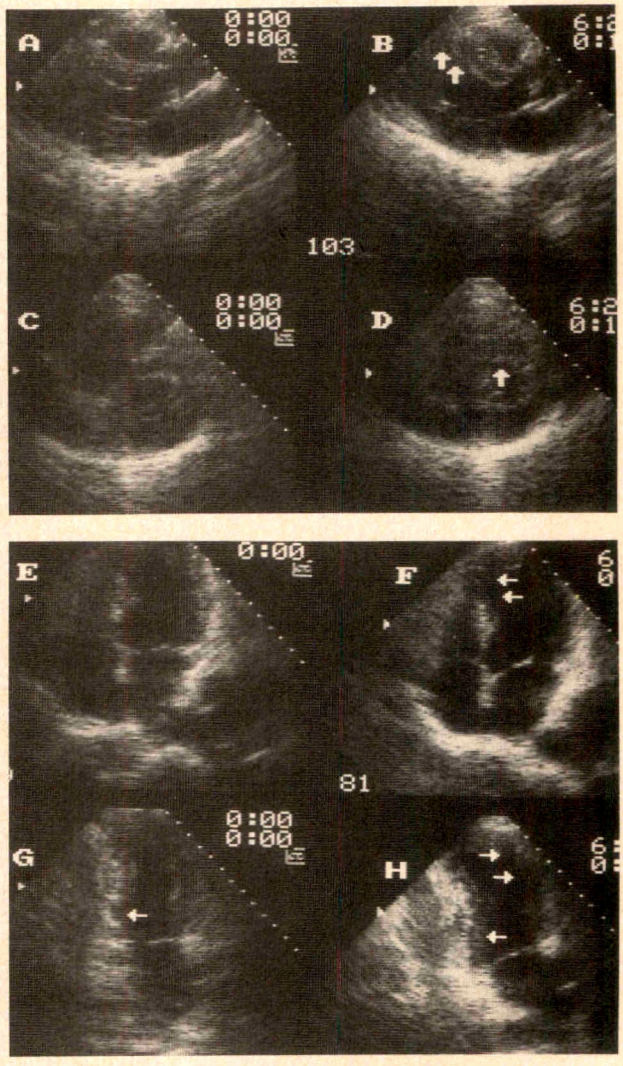


FIGURE 4. Rest and postexercise echocardiograms from a patient who had undergone sequential saphenous vein graft bypass of severe first diagonal and mid-left anterior descending stenoses 2 years previously (presented in same format as Figure 3). Patient developed exertional interscapular ache but had a normal stress electrocardiogram. The resting echocardiograms show severe anteroapical hypokinesia. After exercise, there is anteroseptal and apical akinesia as well as akinesia of the inferior wall *(arrows)*. Angiography indicated that the vein graft was patent to its first anastomosis with the diagonal branch, but the segment that continued to the left anterior descending artery was occluded. In addition, a new 70% stenosis in the mid-right coronary artery was identified.

defined patient populations (those with and without compromise, respectively), such selection bias should not affect these parameters.

Conventionally, coronary stenoses are not judged to be severe unless the vascular luminal diameter is narrowed by ≥70%. However, we and others have found that exercise echocardiography regularly detects provoked regional wall motion abnormalities in the distribution of stenoses as "mild" as 50% (reducing the cross-sectional area by 75%). Based on this collective experience, the 50% severity figure was used in the present report.

Exercise echocardiography predicts the status of regional myocardial vascular supply by evaluating the effect of exercise-provoked augmentation of oxygen demand on regional wall motion. In patients with previous myocardial infarction, it is difficult to define a normal response in the infarct zone. If the akinetic segment represents healed transmural infarction, then its contractile function will not improve even with a normal vascular supply. If the akinetic segment is viable but subserved by a stenosed graft or artery, it, too, will fail to demonstrate augmented contraction with exercise. Because exercise echocardiography depicts changes in regional wall motion and cannot specifically assess viability, we found that this test is not reliable in predicting the status of the vascular supply to the akinetic infarct zone in patients with previous transmural infarction, unless there was some improvement in the contraction of that zone after exercise. Therefore, in this study, infarct-related akinesia, which did not change with exercise, was excluded from analysis.

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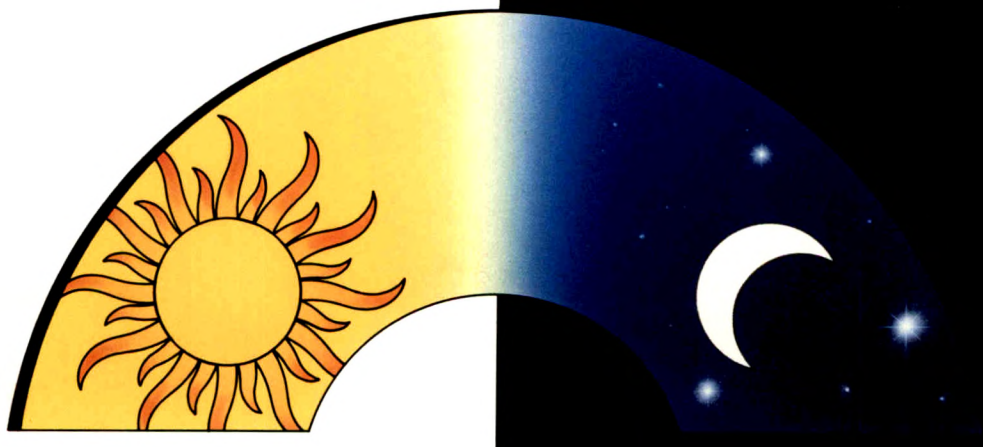
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BRIEF SUMMARY

USE IN PREGNANCY

When used in pregnancy during the second and third trimesters, ACE inhibitors can cause injury and even death to the developing fetus. When pregnancy is detected, ALTACE should be discontinued as soon as possible. **See WARNINGS: Fetal/neonatal morbidity and mortality.**

ALTACE is available in potencies of 1.25 mg, 2.5 mg, 5 mg, and 10 mg in color-coded, hard gelatin capsules.

INDICATIONS AND USAGE: ALTACE is indicated for the treatment of hypertension. It may be used alone or in combination with thiazide diuretics.

In using ALTACE, consideration should be given to the fact that another angiotensin converting enzyme inhibitor, captopril, has caused agranulocytosis, particularly in patients with renal impairment or collagen-vascular disease. Available data are insufficient to show that ALTACE does not have a similar risk. (See WARNINGS.)

CONTRAINDICATIONS: ALTACE is contraindicated in patients who are hypersensitive to this product and in patients with history of angioneurotic edema.

WARNINGS: ***Angioedema:*** Angioedema of the face, extremities, lips, tongue, glottis, and larynx has been reported in patients treated with angiotensin converting enzyme inhibitors. Angioedema associated with laryngeal edema can be fatal. If laryngeal stridor or angioedema of the face, tongue, or glottis occurs, treatment with ALTACE should be discontinued and appropriate therapy instituted immediately. **Where there is involvement of the tongue, glottis, or larynx, likely to cause airway obstruction, appropriate therapy, e.g., subcutaneous epinephrine solution 1:1,000 (0.3 ml to 0.5 ml) should be promptly administered.** (See ADVERSE REACTIONS.)

Hypotension: ALTACE can cause symptomatic hypotension, after either the initial dose or a later dose when the dosage has been increased. Like other ACE inhibitors, ramipril has been only rarely associated with hypotension in uncomplicated hypertensive patients. Symptomatic hypotension is most likely to occur in patients who have been volume- and/or salt-depleted as a result of prolonged diuretic therapy, dietary salt restriction, dialysis, diarrhea, or vomiting. Volume and/or salt depletion should be corrected before initiating therapy with ALTACE.

In patients with congestive heart failure, with or without associated renal insufficiency, ACE inhibitor therapy may cause excessive hypotension, which may be associated with oliguria or azotemia and, rarely, with acute renal failure and death. In such patients, ALTACE therapy should be started under close medical supervision; they should be followed closely for the first 2 weeks of treatment and whenever the dose of ramipril or diuretic is increased.

If hypotension occurs, the patient should be placed in a supine position and, if necessary, treated with intravenous infusion of physiological saline. ALTACE treatment usually can be continued following restoration of blood pressure and volume.

Neutropenia/Agranulocytosis: Another angiotensin converting enzyme inhibitor, captopril, has been shown to cause agranulocytosis and bone marrow depression, rarely in uncomplicated patients, but more frequently in patients with renal impairment, especially if they also have a collagen-vascular disease such as systemic lupus erythematosus or scleroderma. Available data from clinical trials of ramipril are insufficient to show that ramipril does not cause agranulocytosis at similar rates. Monitoring of white blood cell counts should be considered in patients with collagen-vascular disease, especially if the disease is associated with impaired renal function.

Fetal/Neonatal Morbidity and Mortality: ACE inhibitors can cause fetal and neonatal morbidity and death when administered to pregnant women. More than 100 cases have been reported in the world literature. When pregnancy is detected, ACE inhibitors should be discontinued as soon as possible.

The use of ACE inhibitors during the second and third trimesters of pregnancy has been associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible and irreversible renal failure, and death. Oligohydramnios has also been reported, presumably resulting from decreased fetal renal function; oligohydramnios in this setting has been associated with fetal limb contractures, craniofacial deformation, and hypoplastic lung development. Prematurity, intrauterine growth retardation, and patent ductus arteriosus have also been reported, although it is not clear whether these occurrences were due to the ACE-inhibitor exposure.

These adverse effects do not appear to have resulted from intrauterine ACE-inhibitor exposure that has been limited to the first trimester. Mothers whose embryos and fetuses are exposed to ACE inhibitors only during the first trimester should be so informed. Nonetheless, when patients become pregnant, physicians should make every effort to discontinue the use of ALTACE as soon as possible.

Rarely (probably less often than once in every thousand pregnancies), no alternative to ACE inhibitors will be found. In these rare cases, the mothers should be apprised of the potential hazards to their fetuses, and serial ultrasound examination should be performed to assess the intra-amniotic environment.

If oligohydramnios is observed, ALTACE should be discontinued unless it is considered lifesaving for the mother. Contraction stress testing (CST), a non-stress test (NST), or biophysical profiling (BPP) may be appropriate depending upon the week of pregnancy. Patients and physicians should be aware, however, that oligohydramnios may not be apparent until after the fetus has sustained irreversible injury.

Infants with histories of *in utero* exposure to ACE inhibitors should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion. Exchange transfusion or dialysis may be required as means of reversing hypotension and/or substituting for disordered renal function. ALTACE, which crosses the placenta, can be removed from the neonatal circulation by these means, but limited experience has not shown that such removal is central to the treatment of these infants.

No teratogenic effects of ALTACE were seen in studies of pregnant rats, rabbits, and cynomolgus monkeys. On a mg/kg basis, the doses used were up to 2,500 times (in rats), 6.25 times (in rabbits), and 1,250 times (in monkeys) the maximum recommended human dose.

PRECAUTIONS: ***General:*** *Impaired Renal Function:* As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients with severe congestive heart failure whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with angiotensin converting enzyme inhibitors, including ALTACE, may be associated with oliguria and/or progressive azotemia and (rarely) with acute renal failure and/or death. In hypertensive patients with unilateral or bilateral renal artery stenosis, increases in blood urea nitrogen and serum creatinine may occur. Experience with another angiotensin converting enzyme inhibitor suggests that these increases are usually reversible upon discontinuation of ALTACE and/or diuretic therapy. In such patients renal function should be monitored during the first few weeks of therapy. Some hypertensive patients with no apparent pre-existing renal vascular disease have developed increases in blood urea nitrogen and serum creatinine, usually minor and transient, especially when ALTACE has been given concomitantly with a diuretic. This is more likely to occur in patients with pre-existing renal impairment. Dosage reduction of ALTACE and/or discontinuation of the diuretic may be required.

Evaluation of the hypertensive patient should always include assessment of renal function.

Hyperkalemia: In clinical trials, hyperkalemia (serum potassium greater than 5.7 mEq/L) occurred in approximately 1% of hypertensive patients receiving ALTACE. In most cases, these were isolated values, which resolved despite continued therapy. None of these patients was discontinued from the trials because of hyperkalemia. Risk factors for the development of hyperkalemia include renal insufficiency, diabetes mellitus, and the concomitant use of potassium-sparing diuretics, potassium supplements, and/or potassium-containing salt substitutes, which should be used cautiously, if at all, with ALTACE. (See DRUG INTERACTIONS.)

Cough: Cough has been reported with the use of ACE inhibitors. Characteristically, the cough is nonproductive, persistent and resolves after discontinuation of therapy. ACE inhibitor-induced cough should be considered as part of the differential diagnosis of cough.

Impaired Liver Function: Since ramipril is primarily metabolized by hepatic esterases to its active moiety, ramiprilat, patients with impaired liver function could develop markedly elevated plasma levels of ramipril. No formal pharmacokinetic studies have been carried out in hypertensive patients with impaired liver function.

Surgery/Anesthesia: In patients undergoing surgery or during anesthesia with agents that produce hypotension, ramipril may block angiotensin II formation that would otherwise occur secondary to compensatory renin release. Hypotension that occurs as a result of this mechanism can be corrected by volume expansion.

Information for Patients: *Angioedema:* Angioedema, including laryngeal edema, can occur with treatment with ACE inhibitors, especially following the first dose. Patients should be so advised and told to report immediately any signs or symptoms suggesting angioedema (swelling of face, eyes, lips, tongue, or difficulty in breathing) and to take no more drug until they have consulted with the prescribing physician.

Symptomatic Hypotension: Patients should be cautioned that lightheadedness can occur, especially during the first days of therapy, and it should be reported. Patients should be told that if syncope occurs, ALTACE™ (ramipril) should be discontinued until the physician has been consulted.

All patients should be cautioned that inadequate fluid intake or excessive perspiration, diarrhea, or vomiting can lead to an excessive fall in blood pressure, with the same consequences of lightheadedness and possible syncope.

Hyperkalemia: Patients should be told not to use salt substitutes containing potassium without consulting their physician.

Neutropenia: Patients should be told to promptly report any indication of infection (e.g., sore throat, fever), which could be a sign of neutropenia.

Pregnancy: Female patients of childbearing age should be told about the consequences of second- and third-trimester exposure to ACE inhibitors, and they should also be told that these consequences do not appear to have resulted from intrauterine ACE-inhibitor exposure that has been limited to the first trimester. These patients should also be asked to report pregnancies to their physicians as soon as possible.

Drug Interactions: *With Diuretics:* Patients on diuretics, especially those in whom diuretic therapy was recently instituted, may occasionally experience an excessive reduction of blood pressure after initiation of therapy with ALTACE. The possibility of hypotensive effects with ALTACE can be minimized by either discontinuing the diuretic or increasing the salt intake prior to initiation of treatment with ALTACE. If this is not possible, the starting dose should be reduced.

With Potassium Supplements and Potassium-Sparing Diuretics: ALTACE can attenuate potassium loss caused by thiazide diuretics. Potassium-sparing diuretics (spironolactone, amiloride, triamterene, and others) or potassium supplements can increase the risk of hyperkalemia. Therefore, if concomitant use of such agents is indicated, they should be given with caution, and the patient's serum potassium should be monitored frequently.

With Lithium: Increased serum lithium levels and symptoms of lithium toxicity have been reported in patients receiving ACE inhibitors during therapy with lithium. These drugs should be coadministered with caution, and frequent monitoring of serum lithium levels is recommended. If a diuretic is also used, the risk of lithium toxicity may be increased.

Other: Neither ALTACE nor its metabolites have been found to interact with food, digoxin, or antacid.

Carcinogenesis, Mutagenesis, Impairment of Fertility: No evidence of a tumorigenic effect was found when ramipril was given by gavage to rats (up to 500 mg/kg/day for 24 months) or to mice (up to 1,000 mg/kg/day for 18 months). Dosages greatly in excess of those recommended for humans produced hypertrophy of the renal juxtaglomerular apparatus in mice, rats, dogs, and monkeys. No mutagenic activity was detected in the Ames test in bacteria, the micronucleus test in mice, unscheduled DNA synthesis in a human cell line, or a forward gene-mutation assay in a Chinese hamster ovary cell line. Several metabolites and degradation products of ramipril were also negative in the Ames test. A study in rats with dosages as great as 500 mg/kg/day did not produce adverse effects on fertility.

Pregnancy: **Pregnancy Categories C (first trimester) and D (second and third trimesters): See WARNINGS: Fetal/neonatal morbidity and mortality.**

Nursing Mothers: Ingestion of a single 10 mg oral dose of ALTACE resulted in undetectable amounts of ramipril and its metabolites in breast milk. However, because multiple doses may produce low milk concentrations that are not predictable from single doses, ALTACE should not be administered to nursing mothers.

Geriatric Use: Of the total number of patients who received ramipril in US clinical studies of ALTACE 11.0% were 65 and over while 0.2% were 75 and over. No overall differences in effectiveness or safety were observed between these patients and younger patients, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

One pharmacokinetic study conducted in hospitalized elderly patients indicated that peak ramiprilat levels and area under the plasma concentration time curve (AUC) for ramiprilat are higher in older patients.

Pediatric Use: Safety and effectiveness in children has not been established.

ADVERSE REACTIONS: ALTACE has been evaluated for safety in over 4,000 patients with hypertension; of these, 1,230 patients were studied in US controlled trials, and 1,107 were studied in foreign controlled trials. Almost 700 of these patients were treated for at least one year. The overall incidence of reported adverse events was similar in ALTACE and placebo patients. The most frequent clinical side effects (possibly or probably related to study drug) reported by patients receiving ALTACE in US placebo-controlled trials were: headache (5.4%), "dizziness" (2.2%) and fatigue or asthenia (2.0%), but only the last was more common in ALTACE patients than in patients given placebo. Generally, the side effects were mild and transient, and there was no relation to total dosage within the range of 1.25 to 20 mg. Discontinuation of therapy because of a side effect was required in approximately 3% of US patients treated with ALTACE. The most common reasons for discontinuation were: cough (1.0%), "dizziness" (0.5%), and impotence (0.4%).

The side effects considered possibly or probably related to study drug that occurred in US placebo-controlled trials in more than 1% of patients treated with ALTACE are shown below.

PATIENTS IN US PLACEBO-CONTROLLED STUDIES

	Altace (N = 651)		Placebo (N = 286)	
	n	%	n	%
Headache	35	5.4	17	5.9
"Dizziness"	14	2.2	9	3.1
Asthenia (Fatigue)	13	2.0	2	0.7
Nausea/ Vomiting	7	1.1	3	1.0

In placebo-controlled trials, there was also an excess of upper respiratory infection and flu syndrome in the ramipril group. As these studies were carried out before the relationship of cough to ACE inhibitors was recognized, some of these events may represent ramipril-induced cough. In a later 1-year study, increased cough was seen in almost 12% of ramipril patients, with about 4% of these patients requiring discontinuation of treatment. Other adverse experiences reported in controlled clinical trials (in less than 1% of ramipril patients), or rarer events seen in postmarketing experience, include the following (In some, a causal relationship to drug use is uncertain.):

Cardiovascular: Symptomatic hypotension (reported in 0.5% of patients in US trials) (see PRECAUTIONS and WARNINGS), syncope (not reported in US trials), angina pectoris, arrhythmia, chest pain, palpitations, myocardial infarction, and cerebrovascular events.

Renal: Some hypertensive patients with no apparent pre-existing renal disease have developed minor, usually transient, increases in blood urea nitrogen and serum creatinine when taking ALTACE, particularly when ALTACE was given concomitantly with a diuretic. (See WARNINGS.)

Angioneurotic Edema: Angioneurotic edema has been reported in 0.3% of patients in US clinical trials. (See WARNINGS.)

Cough: A tickling, dry, persistent, nonproductive cough has been reported with the use of ACE inhibitors. Approximately 1% of patients treated with ALTACE have required discontinuation because of cough. The cough disappears shortly after discontinuation of treatment. (See PRECAUTIONS.)

Gastrointestinal: Abdominal pain (sometimes with enzyme changes suggesting pancreatitis), anorexia, constipation, diarrhea, dry mouth, dyspepsia, dysphagia, gastroenteritis, nausea, increased salivation, taste disturbance, and vomiting.

Dermatologic: Apparent hypersensitivity reactions (manifested by dermatitis, pruritus, or rash, with or without fever), photosensitivity, and purpura.

Neurologic and Psychiatric: Anxiety, amnesia, convulsions, depression, hearing loss, insomnia, nervousness, neuralgia, neuropathy, paresthesia, somnolence, tinnitus, tremor, vertigo, and vision disturbances.

Fetal/Neonatal Morbidity and Mortality: See WARNINGS: Fetal/neonatal morbidity and mortality.

Other: arthralgia, arthritis, dyspnea, edema, epistaxis, impotence, increased sweating, malaise, myalgia, and weight gain.

Clinical Laboratory Test Findings: *Creatinine and Blood Urea Nitrogen:* Increases in creatinine levels occurred in 1.2% of patients receiving ALTACE alone, and in 1.5% of patients receiving ALTACE and a diuretic. Increases in blood urea nitrogen levels occurred in 0.5% of patients receiving ALTACE alone and in 3% of patients receiving ALTACE with a diuretic. None of these increases required discontinuation of treatment. Increases in these laboratory values are more likely to occur in patients with renal insufficiency or those pretreated with a diuretic and, based on experience with other ACE inhibitors, would be expected to be especially likely in patients with renal artery stenosis. (See PRECAUTIONS and WARNINGS.)

Since ramipril decreases aldosterone secretion, elevation of serum potassium can occur. Potassium supplements and potassium-sparing diuretics should be given with caution, and the patient's serum potassium should be monitored frequently. (See PRECAUTIONS and WARNINGS.)

Hemoglobin and Hematocrit: Decreases in hemoglobin or hematocrit (a low value and a decrease of 5 g/dl or 5% respectively) were rare, occurring in 0.4% of patients receiving ALTACE alone and in 1.5% of patients receiving ALTACE plus a diuretic. No US patients discontinued treatment because of decreases in hemoglobin or hematocrit.

Other (causal relationships unknown): Clinically important changes in standard laboratory tests were rarely associated with ALTACE administration. Elevations of liver enzymes, serum bilirubin, uric acid, and blood glucose have been reported, as have scattered incidents of leukopenia, eosinophilia, and proteinuria. In US trials, less than 0.2% of patients discontinued treatment for laboratory abnormalities: all of these were cases of proteinuria or abnormal liver-function tests.

OVERDOSAGE: Human overdoses of ramipril have not been reported, but the most common manifestation of human ramipril overdosage is likely to be hypotension. Because the hypotensive effect of ramipril is achieved through vasodilation and effective hypovolemia, it is reasonable to treat ramipril overdose by infusion of normal saline solution.

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Effect of Maximal Medical Therapy on Refractoriness of Unstable Angina Pectoris

David W. Grambow, MD, and Eric J. Topol, MD

A group of 125 patients with unstable angina were studied over a 5-year period to define the incidence of refractory unstable angina in the current era of 5-drug medical therapy with intravenous heparin, aspirin, nitrates, calcium antagonists and β blockers. All patients had >20 minutes of chest pain at rest with reversible electrocardiographic changes occurring in the absence of myocardial infarction. Patients were considered refractory only if chest pain continued despite treatment with maximal 5-drug therapy.

At the time of transfer to the center, 65 patients continued to have ischemic chest pain at rest and were considered "medically refractory" by their referring physicians. A more aggressive medical regimen was used, and 54 patients (83%) were rendered chest pain–free. Of the 11 truly refractory patients (8.8%), coronary arteriography revealed an increased likelihood of left main or 3-vessel disease (7 of 11 vs 26 of 114; p = 0.01). In-hospital treatment strategies for the 114 patients stabilized with medical therapy included continued medical therapy (n = 37), coronary angioplasty (n = 46) and bypass grafting (n = 31). The rate of myocardial infarction or death in patients managed medically was 3%. Coronary angioplasty in medically stabilized patients was complicated by an abrupt closure rate of 26%, and a 17% rate of myocardial infarction, death or need for emergency bypass grafting. Medically stabilized patients undergoing bypass grafting had a 9% rate of myocardial infarction or death. Unstable angina truly refractory to current, maximal medical therapy is infrequent (8.8%). However, the refractory group is vulnerable to adverse angioplasty results and cardiac events.

(Am J Cardiol 1992;70:577–581)

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Unstable angina pectoris is responsible for >750,000 hospitalizations annually in the United States.[1] With conventional antianginal therapy, up to 15% of patients develop myocardial infarction in the hospital.[2] Recent studies suggest that routine use of intravenous heparin and aspirin significantly reduces morbidity and mortality in patients hospitalized with unstable angina.[3,4] Urgent revascularization by coronary angioplasty or bypass grafting has an increased complication rate in patients with unstable angina pectoris.[5,6] However, patients with unstable angina refractory to medical therapy are at high risk for in-hospital cardiac events and should be most strongly considered for urgent revascularization. The incidence and outcomes of refractory unstable angina in the contemporary setting of maximal antianginal, antiplatelet and anticoagulant therapy is unknown. We sought to define the incidence of refractory unstable angina in a group of patients with unstable angina transferred to our tertiary care facility for consideration of coronary revascularization.

METHODS

Selection of patients: Five hundred and two patients referred to the University of Michigan Hospital with the diagnosis of unstable angina between January 1, 1986 and January 1, 1991 were analyzed retrospectively. Patients were included in the study provided that they: (1) were transferred from an outside hospital after being admitted with chest pain at rest of >20 minutes duration; (2) had reversible electrocardiographic changes with chest pain, including >1 mm ST-segment depression or elevation or T-wave inversion in 2 limb or contiguous precordial leads; (3) had peak creatine kinase levels <2 times the upper limits of normal; and (4) underwent an attempt at medical stabilization before transfer.

One hundred twenty-five patients fulfilled the inclusion criteria and constituted the study population (Figure 1). Baseline data abstracted from the clinical record on these patients included: (1) history of stable angina pectoris, myocardial infarction or congestive heart failure; (2) history of myocardial revascularization; (3) character and location of electrocardiographic changes with chest pain; (4) medical regimen at transfer; (5) maximal medical regimen at University of Michigan; (6) duration of medical therapy before resolution of chest pain or before patient was considered refractory; and (7) results of cardiac catheterization including coronary anatomy (stenoses considered significant if ≥70%) and left ventricular ejection fraction.

Maximal medical therapy: Maximal medical therapy was considered treatment with a combination of as-

TABLE I Characteristics of Patients with Refractory Unstable Angina and Those Stabilized with Medical Therapy

	Refractory (n = 11)	Medically Stabilized (n = 114)	p Value
Age (year)	68 ± 10	64 ± 11	NS
Male gender	7 (64%)	61 (54%)	NS
Prior stable angina	7 (64%)	83 (73%)	NS
Prior myocardial infarction	4 (36%)	48 (42%)	NS
Prior coronary bypass surgery	5 (45%)	20 (18%)	0.07
Ejection fraction (%)	43 ± 13	51 ± 13	NS
Duration of pain at rest (days)	9 ± 4	4 ± 4	0.01
ST-segment changes			
ST elevation	2 (18%)	11 (9%)	NS
ST depression	7 (64%)	42 (37%)	NS
T-wave inversion	2 (18%)	61 (54%)	0.05
Anterior changes	7 (64%)	25 (22%)	0.008
Inferior changes	0	43 (38%)	0.03
Lateral changes	4 (36%)	46 (40%)	NS
Coronary anatomy			
Left main or 3-vessel disease	7 (64%)	26 (23%)	0.01
1- to 2-vessel disease	4 (36%)	88 (77%)	0.01
In-hospital death or myocardial infarction	4 (36%)	9 (8%)	0.009

NS = not significant.

pirin, intravenous heparin, nitrates, β blockers and calcium antagonists. The number of these agents a patient was receiving was noted. Patients were considered to have true refractory unstable angina if chest pain at rest continued despite treatment with all 5 classes of medication at maximal hemodynamically tolerated doses.

Patient groups: Patients were classified as medically refractory if chest pain and electrocardiographic changes persisted with maximal medical therapy, or as medically stabilized if chest pain resolved with medical therapy. Medically stabilized patients were further classified based on subsequent in-hospital treatment strategy, which included continued medical therapy, coronary angioplasty and bypass grafting. In-hospital recurrent angina, myocardial infarction or death were recorded for each treatment strategy.

Statistical analysis: For discrete variables, analysis was performed with chi-square tests and for continuous variables, Student *t* tests were used. All group data were expressed as mean ± 1 SD. A p value <0.05 was considered statistically significant.

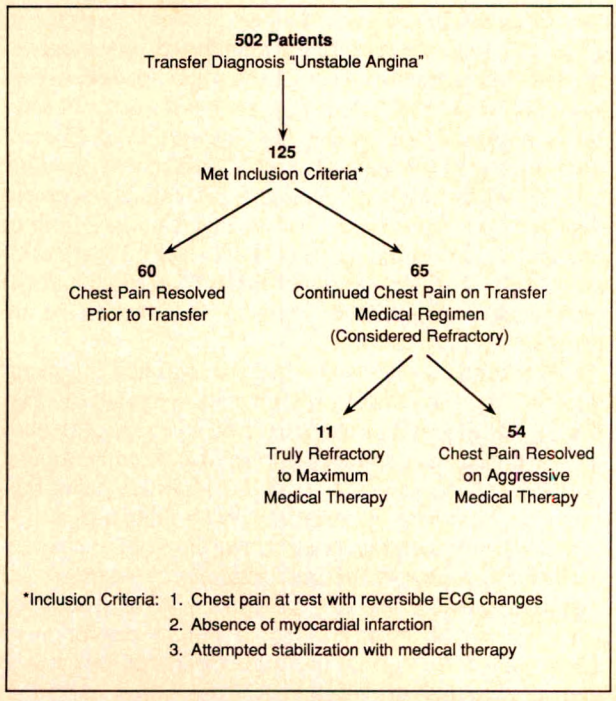


FIGURE 1. Outline of study population. Only 11 of 125 patients (8.8%) with chest pain at rest and reversible electrocardiographic (ECG) changes were refractory to maximal medical therapy, including treatment with aspirin, intravenous heparin, nitrates, calcium antagonists and β blockers.

RESULTS

In all, 502 patients with "unstable angina" were transferred to the University of Michigan Hospital during the study period (Figure 1). The following groups of patients were excluded from this cohort: 17 transferred directly for revascularization without attempts at medical stabilization; 28 with evidence of myocardial infarction; 51 without chest pain at rest; and 281 after review of the records did not document reversible electrocardiographic changes with chest pain. Inclusion criteria were fulfilled by 125 patients. Chest pain resolved with medical therapy in 60 of these patients before transfer. Chest pain at rest with ischemic electrocardiographic changes continued in 65 patients who were considered medically refractory by their referring physicians. A more aggressive medical regimen was used at the University of Michigan, and 54 (83%) of these patients became free of chest pain. Only 11 patients (8.8%) ultimately proved refractory to maximal medical therapy.

Demographic and clinical data: Table I shows characteristics of the 11 patients with refractory unstable angina compared with the 114 who stabilized with medical therapy. No significant differences were found between the groups regarding age, sex, history of stable angina pectoris or myocardial infarction, and left ventricular function. Patients with refractory unstable angina were more likely to have had prior coronary artery bypass grafting. Patients with refractory unstable angina had persistent chest pain despite an average of 9 days of maximal (5-drug) medical therapy, whereas those responding to medical therapy with resolution of chest pain did so in an average of 4 days (p = 0.01). Patients with refractory unstable angina were more likely to have anterior electrocardiographic changes with chest pain (7 of 11 vs 25 of 114; p = 0.008). Inferior electrocardiographic changes with chest pain were not seen in the refractory group (p = 0.03). T-wave inversion with chest pain was more often seen in patients who stabilized on medical therapy (p = 0.05). All patients underwent cardiac catheterization. Refractory patients had an increased likelihood of left main or 3-vessel coronary artery disease (7 of 11 vs 26 of 114; p = 0.01). A >70% stenosis of the left main coronary artery was identified in 5 of 11 patients in the refractory group and in 2 of 114 in the medically stabilized group. In-hospital myocardial infarction or death was significantly more frequent in the refractory group (4 of 11 vs 9 of 114; p = 0.009).

TABLE II Comparison of Medical Regimens at Community Hospitals and University of Michigan in 65 Patients Considered to Have Medically Refractory Unstable Angina at Transfer

	Community Hospitals (n = 65)	University of Michigan (n = 65)
Aspirin	46 (71%)	64 (99%)
Intravenous heparin	21 (32%)	47 (72%)
Intravenous nitroglycerin	15 (23%)	34 (52%)
Oral/topical nitrates	40 (62%)	29 (45%)
Calcium antagonists	53 (82%)	61 (94%)
β blockers	19 (19%)	34 (52%)
1-drug therapy*	6 (9%)	0
2-drug therapy*	16 (25%)	2 (3%)
3-drug therapy*	24 (37%)	13 (20%)
4-drug therapy*	12 (18%)	23 (35%)
5-drug therapy*	7 (11%)	27 (42%)

*Drug therapy is considered treatment with combinations of aspirin, intravenous heparin, nitrates, calcium antagonists and β blockers.

TABLE III Baseline Characteristics of 114 Patients with Unstable Angina Stabilized with Medical Therapy

	In-Hospital Treatment Strategy		
	Medical Management (n = 37)	Angioplasty (n = 46)	Bypass Surgery (n = 31)
Days of medical therapy before stabilization	4	3	5
No. of drugs used at stabilization*			
1 to 3	17 (46%)	20 (43%)	13 (42%)
4 or 5	20 (54%)	26 (57%)	18 (58%)
Coronary artery disease			
1- to 2-vessel	30 (81%)	41 (89%)	13 (42%)
3-vessel or left main	7 (19%)	5 (9%)	18 (58%)
Ejection fraction	51 ± 15	53 ± 19	47 ± 11
Prior coronary bypass surgery	9 (24%)	7 (15%)	3 (10%)

*Drug therapy is considered treatment with combinations of aspirin, intravenous heparin, nitrates, calcium antagonists and β blockers; values are mean ±SD.

Comparison of medical regimens: Table II compares the medical regimens at community hospitals and at the University of Michigan in the 65 patients considered to have medically refractory unstable angina at the time of transfer. Resolution of chest pain at the University of Michigan was achieved in 54 of 65 patients (83%) with more frequent use of aspirin, and intravenous heparin and nitroglycerin. Multidrug therapy using combinations of aspirin, intravenous heparin, nitrates, calcium antagonists and β blockers was also more frequent at the University of Michigan (50 of 65 patients [77%] receiving 4- or 5-drug therapy vs 19 of 65 [29%] at community hospitals; $p = 0.0001$).

Hospital course (refractory unstable angina patients): All 11 patients with refractory unstable angina underwent revascularization. Coronary angioplasty was performed in 4 patients with refractory angina. One patient had abrupt closure and subsequent non-Q-wave myocardial infarction. One patient with a large dissection of the left anterior descending coronary artery died the day after angioplasty with a cardiac arrest. There were 7 refractory patients treated with bypass grafting. Two patients died after surgery; 1 could not be weaned from cardiopulmonary bypass, and 1 died 1 day after surgery from ventricular fibrillation. One patient had a perioperative myocardial infarction.

Hospital course (stabilized patients): The hospital course of the 114 medically stabilized patients included continued medical therapy in 37, coronary angioplasty in 46, and bypass grafting in 31. Table III shows that the groups were similar in duration of medical therapy before resolution of chest pain, number of drugs used to achieve medical stabilization, and left ventricular function. Patients with left main or 3-vessel coronary artery disease were more likely to undergo bypass grafting during hospitalization, whereas those with 1- or 2-vessel coronary artery disease were more often treated with continued medical therapy or coronary angioplasty.

Table IV shows the hospital course of the 114 patients with unstable angina who became free of chest pain with medical therapy. Stabilized patients managed with continued medical therapy (n = 37) were chest pain–free an average of 7 days before discharge. No patient in this group had a myocardial infarction and 1 (2.7%) died during hospitalization. Recurrent stable angina developed in 3 patients (8.1%) and was controlled by alterations in medical therapy.

TABLE IV Hospital Course of 114 Patients with Unstable Angina Stabilized with Medical Therapy

	In-Hospital Treatment Strategy		
Clinical Outcomes	Medical Management (n = 37)	Angioplasty (n = 46)	Bypass Surgery (n = 31)
Myocardial infarction	0	4 (9%)	1 (3%)
Death	1 (3%)	1 (2%)	2 (6%)
No. of drugs at discharge*			
1 or 2	14 (39%)	21 (47%)	18 (58%)
3 or 4	22 (61%)	24 (53%)	11 (40%)

*Includes combinations of aspirin, nitrates, calcium antagonists and β blockers.

Coronary angioplasty was performed in 46 medically stabilized patients before discharge. Indications for coronary angioplasty included: (1) coronary anatomy considered high risk for future cardiac events (n = 42; 91%); (2) ischemia on predischarge exercise testing (n = 3; 6.7%); and (3) recurrent exertional angina (n = 1; 2.2%). Coronary angioplasty was performed an average of 6 days after the onset of unstable angina and 4 days after the last episode of chest pain. Angioplasty was successful in 92% of cases. Abrupt closure complicated 12 of 46 procedures (26%). Emergency bypass grafting was needed in 3 patients (6.5%), 4 (8.7%) had postprocedural myocardial infarction, and 1 (2.2%) died after angioplasty. After angioplasty, the incidence of emergency bypass grafting, myocardial infarction or death was 17%.

Bypass grafting was performed in 31 medically stabilized patients before discharge. Indications for surgery included: (1) coronary anatomy considered high risk for future cardiac events (n = 26; 84%); (2) ischemia on predischarge exercise testing (n = 2; 6%); and (3) recurrent exertional angina (n = 3; 10%). One patient had a

perioperative myocardial infarction, and there were 2 deaths after surgery.

Myocardial infarction or death occurred in 3% of patients managed medically, in 11% treated with coronary angioplasty and in 9% who underwent bypass grafting. Patients revascularized by coronary angioplasty or bypass grafting tended to be discharged with less medical therapy.

DISCUSSION

Atherosclerotic plaque rupture with concomitant platelet aggregation and thrombus formation is believed to be the underlying mechanism for the development of acute coronary syndromes.[7,8] Most studies assessing morbidity and mortality in patients hospitalized with unstable angina were performed before routine use of intravenous heparin and aspirin. Conventional therapy of patients hospitalized with unstable angina with nitrates, β blockers or calcium antagonists reduces the number of ischemic episodes, but does not reduce the frequency of myocardial infarction (13%) or death (4%).[9–13] Both aspirin[3,4,12,13] and intravenous heparin[3,4] have been shown to reduce the rate of myocardial infarction and death in patients hospitalized with unstable angina.

Our findings show that "true" refractory unstable angina is infrequent (<9%) with aggressive contemporary medical therapy, including combinations of antianginal, anticoagulant and antiplatelet agents. Theroux et al[3] showed a 23% incidence of refractory angina in patients hospitalized with resting or accelerating angina managed with nitrates, β blockers or calcium antagonists. When intravenous heparin with or without aspirin was used, a 9.6% incidence of refractory angina was observed. Most patients in our study considered medically refractory at transfer were medically undertreated. Of patients considered medically refractory who were transferred to our hospital for urgent revascularization, most (83%) became free of chest pain on a more aggressive medical regimen. Only one third of these pseudorefractory patients were receiving intravenous heparin, and surprisingly, 30% were not receiving aspirin therapy.

Persistence of chest pain in patients hospitalized with unstable angina despite maximal medical therapy predicts a poor outcome, with a 51% incidence of early infarction or death.[14] All refractory patients in this study underwent revascularization by either coronary angioplasty or bypass grafting. However, a 36% rate of in-hospital myocardial infarction or death was still observed.

The hospital treatment strategies for medically stabilized patients included continued medical management, coronary angioplasty and bypass grafting. Several prior studies showed that patients with unstable angina who become chest pain–free with medical therapy have a low rate of in-hospital cardiac events, with a 1 to 2% mortality rate and a 7 to 9% rate of myocardial infarction.[14,15] In the study by Theroux et al[3] and the Research Group on Instability in Coronary Artery Disease in Southeast Sweden (RISC) trial,[4] the use of intravenous heparin and aspirin in combination with antianginal therapy in the treatment of patients hospitalized with unstable angina resulted in a 1.5% rate of myocardial infarction or death. Medically stabilized patients in our study whose treatment strategy consisted of continued medical therapy had a low rate (30%) of in-hospital myocardial infarction or death. Rapid progression of the underlying coronary stenosis is known to occur in most patients after an episode of unstable angina, with 30 to 50% redeveloping angina and crossing over to revascularization by 1 year.[16] Frequently cited predictors of poor long-term outcome in patients with unstable angina managed medically include left main or 3-vessel coronary artery disease, decreased left ventricular function, abnormal baseline electrocardiogram, prior myocardial infarction, reperfusion abnormality on thallium imaging, and silent ischemia on continuous ambulatory monitoring.[17–20] Thus, although most patients hospitalized with unstable angina do not need urgent revascularization for relief of chest pain, recurrent anginal symptoms after discharge are common.

Coronary angioplasty within the first 1 to 2 weeks after the onset of unstable angina has an increased complication rate.[5,16,21–26] Angioplasty in this setting of intraluminal thrombus[27] carries a significantly higher rate of abrupt closure.[28] A review of the studies of coronary angioplasty in unstable angina shows a major complication rate (myocardial infarction, emergent bypass grafting or death) of 10 to 26%.[5,16,21–26] Treatment of these patients with 3 to 5 days of intravenous heparin in preparation for coronary angioplasty may decrease this complication rate.[29,30] Myler et al[5] found that angioplasty in patients within the first 2 weeks after the onset of unstable angina is associated with a lower initial success rate and a two- to threefold increased risk for myocardial infarction, need for emergency bypass grafting, death or development of late recurrent angina. The high complication rate and poor outcome for coronary angioplasty in patients with unstable angina in our study (26% abrupt closure rate, and 17% incidence of myocardial infarction, emergency bypass grafting or death) supports the contention that early coronary angioplasty in unstable angina has a complication event rate that may exceed the natural history of adverse cardiac events occurring in this population when managed conservatively with medical therapy.[23] An increased operative mortality has also been reported when coronary artery bypass grafting is performed in patients with unstable angina.[6] The rate of myocardial infarction or death in this study for medically stabilized patients undergoing bypass grafting before hospital discharge was 9%.

Comparisons between treatment strategies (medical management, coronary angioplasty and bypass grafting) of the medically stabilized patients are not possible, because of the retrospective nature of this study. Because our hospital serves as a referral center, the characteristics of patients with unstable angina in this study may differ from those presenting to other hospitals. Furthermore, with the inclusion criteria selecting only patients with prolonged angina at rest and electrocardiographic changes, the high complication rate of coronary angioplasty may not reflect the results of angioplasty in patients with new-onset or accelerating unsta-

ble angina pectoris. Finally, the data are limited by the absence of long-term follow-up and thus only provide a "window" of the acute phase of this clinical syndrome.

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Normalization of Impaired Response of Platelets to Prostaglandin E_1/I_2 and Synthesis of Prostacyclin by Insulin in Unstable Angina Pectoris and in Acute Myocardial Infarction

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The minimal inhibitory concentration of prostaglandin E_1 (used as a probe for prostacyclin [PGI_2]) needed to inhibit platelet aggregation (36 ± 16 nM) in normal volunteers (n = 40) increased (64 ± 30 nM) in patients (n = 46) with acute coronary artery disease. Bolus injection of insulin in 20 patients, 0.1 U/kg body weight 4 times a day (every 6 hours) for 7 days decreased the minimal inhibitory concentration of prostaglandin E_1 from 64 ± 30 to 26 ± 12 nM ($p < 0.001$). Twenty other patients who received only saline solution had no decrease in minimal inhibitory concentration of the prostanoid. The bolus injection of insulin also increased the plasma level of PGI_2 (9 ± 2 pM) twofold in these patients (28 ± 10 pM). Administration of aspirin inhibited the insulin-induced increase of plasma prostanoid level. Patients in the placebo group had no increase in plasma PGI_2 level. The bolus injection of insulin administered only once to another group of patients (n = 6) demonstrated that the hormonal effects were maximally increased within an hour of insulin administration, and were directly related to the increased insulin level in plasma. These results indicated the feasibility of using physiologic quantities of insulin for controlling of platelet aggregation through resensitization of platelet response to prostaglandin and increased synthesis of PGI_2 in vivo in acute coronary artery disease.

(Am J Cardiol 1992;70:582–586)

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Aggregation of platelets by aggregating agents like thrombin, 1-epinephrine, adenosine diphosphate or collagen is critically important both in normal hemostasis and in the development of thrombosis.[1] The aggregation of platelets is inhibited by autacoids like prostaglandin E_1 (PGE_1) and prostacyclin (PGI_2) through the increase in cyclic adenosine monophosphate.[2–5] Hyperactivity of platelets, and their adhesion and aggregation at the site of injury in the atherosclerotic vessel wall have been demonstrated to be crucially important in the development of thrombosis in coronary artery disease.[6–11] Although PGI_2 through its inhibitory effect on platelet aggregation is believed to be beneficial in preventing thrombosis,[12] clinical trials of the prostanoid to control platelet aggregation in these patients has proved disappointing.[13–15] Treatment of platelets with physiologic amounts of insulin (100 to 200 μU/ml) in vitro decreases the inhibitory concentration of prostaglandin through increased binding of PGE_1/I_2.[16,17] As an alternate approach to "normalize" the impaired response of platelets to the inhibitory effect of prostaglandin in coronary artery disease, we administered insulin to these patients, and determined the effect of the hormone on the response of platelets to prostaglandin.

METHODS

Ethical clearance: The protocol was approved by the Institutional Review Board for Clinical Research, Montefiore Medical Center, Bronx, New York, and the National Institute of Cardiovascular Disease, Karachi, Pakistan.

Patients: Two categories of patients were studied: (1) patients with unstable angina pectoris, and (2) patients with acute myocardial infarction. Unstable angina pectoris was defined as: (1) severe angina at rest for more than 10 to 15 minutes but <30 minutes; (2) transient ST-segment or T-wave changes, or both, in ≥2 contiguous leads in the electrocardiogram or, if electrocardiographic changes were not present, documentation of coronary artery disease, no elevation of plasma creatine kinase and no appearance of creatine kinase-MB isoenzyme in plasma. Acute myocardial infarction was characterized as: (1) chest pain characteristic of myocardial ischemia for ≥30 minutes; (2) ST-segment elevation of ≥2 leads in the electrocardiogram, reflecting a single myocardial region; and (3) confirmation of the

diagnosis of acute myocardial infarction by elevated creatine kinase level and by creatine kinase-MB isoenzyme in plasma.

All patients studied were admitted to the coronary care unit of the National Institute of Cardiovascular Disease, Karachi, Pakistan.

Patient group and outline of protocol: To determine the effect of increased plasma levels of insulin on platelet prostaglandin sensitivity and PGI_2 synthesis, patients were randomized and subdivided into 3 groups. (1) experimental group A: These patients received repeated injection of insulin for 7 days as described. (2) experimental group B: These patients received insulin for 1 time only. (3) placebo group: They received saline solution only for 7 days. Experimental group A consisted of 20 patients (14 men and 6 women, aged 35 to 59 years, median 48). Eight had unstable angina pectoris and 12 had acute myocardial infarction. Experimental group B consisted of 6 patients (3 women and 3 men, aged 42 to 55 years, median 51). Two had unstable angina pectoris and 4 had acute myocardial infarction. This group was included in the study in order to determine the effect of a transient increase in plasma insulin on minimal inhibitory concentration of PGE_1 to inhibit platelet aggregation and plasma PGI_2 levels. The placebo group had 20 patients (13 men and 7 women aged 36 to 56 years, median 49), and served as the control group. Twelve had unstable angina pectoris and 8 had acute myocardial infarction. None of these patients had a history of hypertension or diabetes mellitus or had taken any medication including aspirin for ≥14 days before hospitalization for severe chest pain.

Concomitant medical therapy: All 46 patients received nitropreparations. Twelve patients with acute myocardial infarction and 7 with unstable angina pectoris received diltiazem. Six patients with acute myocardial infarction and 3 with unstable angina pectoris received intravenous infusion of heparin to keep the partial thromboplastin time 1.5 to 2 times above the control level. Most of the patients also received diazepam. Potassium (Slow K®, CIBA) was given to all patients (600 mg/day potassium chloride). Unless otherwise stated none of these patients took any aspirin during the study.

Normal volunteers: Forty normal volunteers (22 men and 18 women aged 30 to 59 years [median 46]) participated in the study. None of the volunteers were smokers, had systemic hypertension or known family history of diabetes mellitus. They took no medication including aspirin for ≥2 weeks before the study.

Administration of insulin and collection of blood: Blood samples (20 to 25 ml) were collected within 2 hours of hospitalization (day 0), before patients received any medication, to determine the basal response of platelets to the inhibitory effect of prostaglandin and plasma PGI_2 levels. Blood was collected in sodium citrate (9 volumes of blood to 1 volume of 0.13 M sodium citrate) from patients by using 19 gauge siliconized needles in plastic tubes. After blood was drawn, the patients in experimental group A received a bolus injection of insulin (0.1 U/kg body weight) every 6 hours for 7 days. Immediately before administration, insulin (Humulin R®, Eli Lily) was mixed with the patient's own blood (0.2 ml) and the syringe was flushed with 0.2 ml of saline solution. After 5 days of the bolus injection of insulin, aspirin (325 mg every 8 hours) was given to 7 of these patients, and the injection of the hormone was continued up to 7 days in all 20 patients. Blood samples were obtained from the patients every 24 hours after the initial injection of the hormone, and inhibition of platelet aggregation and plasma PGI_2 levels were determined. During the entire period, care was taken to ensure that the blood glucose level did not fall below 80 mg/dl. If necessary, the glucose level was maintained by injecting up to 10.0 g dextrose in 50% solution (Bristol). In the experimental Group B patients, who received the bolus injection of insulin only once, blood samples were collected at 0, 20 and 30 minutes, and 1, 2 and 4 hours after the injection of the hormone, and the minimal inhibitory concentration of PGE_1 and plasma PGI_2 concentration were determined. In the placebo group, blood was drawn in a similar manner except that these patients received saline solution only.

Platelet aggregation studies: Immediately after blood was collected, platelet-rich plasma was prepared and platelet aggregation was studied by using an aggregometer as described.[17] The inhibition of platelet aggregation by prostaglandin was studied by adding varying amounts of PGE_1 as a probe for the interaction of both PGI_2 and PGE_1 to platelet prostaglandin receptor[5] as described previously.[16] Minimal inhibitory concentration is defined as the minimal amount of PGE_1 that will completely inhibit platelet aggregation induced by a minimal quantity of adenosine diphosphate capable of causing maximal platelet aggregation.

Plasma prostaglandin level: Plasma PGI_2 level was determined in its 6-keto prostaglandin $F_{1\alpha}$ (6-keto-$PGF_{1\alpha}$) form by using a radioimmunoassay kit from New England Nuclear, Boston, Massachusetts. Typically, plasma samples in 1 mM ethylenediaminetetraacetic acid were treated with 1.0 N hydrochloric acid (final), extracted, and quantitated by radioimmunoassay.[18]

Determination of platelet cyclic adenosine monophosphate content: Washed platelets (2×10^8 cells) were incubated with 10 mM theophylline for 3 minutes at 23°C before the addition of 1.0 μM PGE_1 in a total volume of 0.4 ml.[17] After a second incubation for 1 minute, the reaction was terminated and the cyclic adenosine monophosphate content of the platelets was determined by protein kinase binding.[18]

Assay of insulin, glucose, potassium and sodium levels in plasma: The plasma insulin level was measured by the method of Yalow & Berson.[19] Glucose was determined by the glucose oxidase method (Glucose I Analyzer, Beckman Instrument). Plasma sodium and potassium levels were measured by an auto analyzer. As needed, the blood glucose level was monitored at the bedside with "ExacTech" (Baxter).

Determination of prothrombin time and activated partial thromboplastin time: Prothrombin time and activated partial thromboplastin time were determined by

the methods described before.[20,21] The patients who received heparin or aspirin were excluded from this study.

Statistical analyses: Results were expressed as mean ± SD. The statistical significance (p value) of the results was evaluated by 2-tailed paired Student's *t* test using a microcomputer.

RESULTS

Plasma insulin and glucose levels in patients with unstable angina pectoris and acute myocardial infarction: On admission, most patients were found to be hyperglycemic (glucose, 136 ± 26 [SD] mg/dl; n = 46). Despite the fact that none of these patients had any history of diabetes mellitus, the plasma insulin level was low (17 ± 10 μU/ml), a value similar to that of fasting normal volunteers (21 ± 11 μU/ml; n = 40). In the placebo group patients (n = 20) who did not receive a bolus injection of insulin, both the hyperglycemic condition (glucose, 135 ± 35 mg/dl) and the low level of insulin (18 ± 9 μU/ml) in the circulation persisted for the entire study period (7 days).

Effect of bolus injection of insulin on platelet response to prostaglandin E_1 in patients with unstable angina pectoris and acute myocardial infarction: The basal response of platelets from these patients to the inhibitory effect of PGE_1 showed that these platelets were significantly resistant to the inhibitory effect of PGE_1. The minimal inhibitory concentration of PGE_1, which was 36 ± 16 nM in the case of platelets from normal volunteers, increased to 64 ± 30 nM in these patients ($p < 0.001$; n = 46). The bolus infusion of insulin in patients with acute coronary artery disease (n = 20) resulted in a significant increase in the sensitivity of these platelets to the inhibitory effect of PGE_1. The infusion of insulin for 5 days to these patients decreased the minimal inhibitory concentration of the prostanoid from 63 ± 30 to 26 ± 12 nM ($p < 0.001$). On day 5, seven of these patients were given aspirin (see below), and they were excluded from the study. However, the minimal inhibitory concentration of PGE_1 for the platelets of the other 13 patients, who received insulin for 7 days, remained significantly lower than that of the placebo group during the study ($p < 0.001$). This decrease in the amounts of PGE_1 needed to inhibit platelet aggregation by the hormone was not gradual, but the maximal effect of insulin was achieved within 24 hours of the administration of the hormone. In contrast, platelets from the placebo group showed persistent resistance to the inhibitory effect of PGE_1 during the same period (Figure 1).

The increased PGE_1 sensitivity of platelets from the patients treated with insulin was found to be related to the increased synthesis of cyclic adenosine monophosphate. The basal cyclic adenosine monophosphate level of platelets before the administration of insulin, which was 2 ± 0.8 pmol/10^8 cells increased to 7 ± 3 pmol/10^8 cells (n = 15) in the presence of 1.0 μM of PGE_1. When these patients were treated with insulin for 24 hours, as previously described, not only the basal cyclic adenosine monophosphate (4 ± 0.5 pmol/10^8 cells) increased ($p < 0.001$), but the synthesis of cyclic adenosine monophosphate in the presence of the same amount of PGE_1 was significantly increased (18 ± 5 pmol/10^8 cells; $p < 0.001$).

Effect of bolus injection of insulin on plasma prostacyclin level in patients with unstable angina pectoris and acute myocardial infarction: Infusion of insulin in these patients not only increased the response of platelets to the inhibitory effect of PGE_1, it also significantly increased the plasma PGI_2 level, measured in its 6-keto-$PGF_{1\alpha}$ form, when compared with the basal level of the

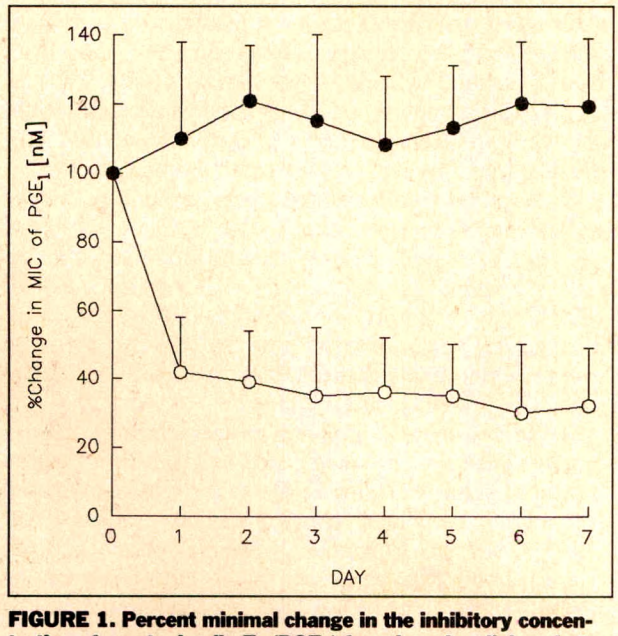


FIGURE 1. Percent minimal change in the inhibitory concentration of prostaglandin E_1 (PGE_1) for adenosine diphosphate–induced platelet aggregation. *Open circles,* platelets from patients who received bolus injection of insulin; *closed circles,* platelets from the placebo group. The number of patients from day 0 to day 5 was 20, and day 5 to day 7 was 13. Seven of the 20 patients received aspirin on day 5, and were excluded from the study. MIC = minimal inhibitory concentration.

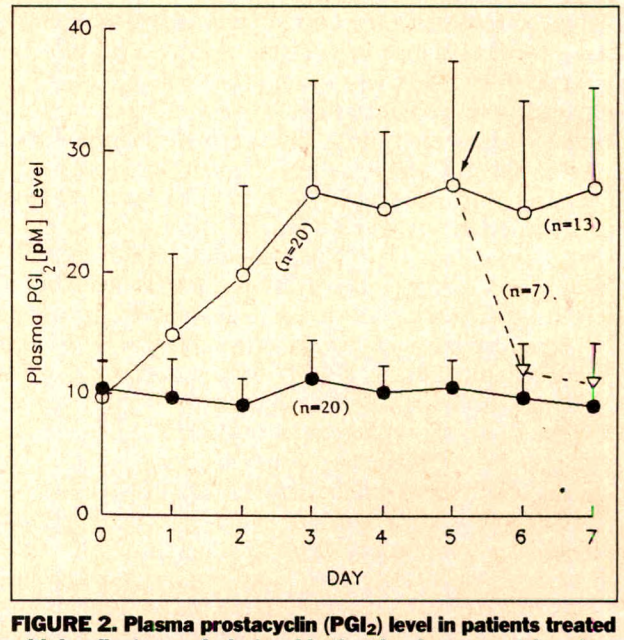


FIGURE 2. Plasma prostacyclin (PGI_2) level in patients treated with insulin *(open circles)* and in the placebo group *(closed circles). Arrow* indicates the beginning of aspirin administration.

prostanoid before the hormone was administered (Figure 2). The basal level of PGI_2 in experimental group A, which was 9 ± 2 pM before the infusion of insulin, was increased nearly threefold (28 ± 10 pM) after 3 days of infusion of the hormone ($p < 0.001$). Administration of aspirin to 7 patients, who also concommitantly received insulin completely inhibited the insulin-induced increase of plasma PGI_2 level. The plasma PGI_2 level in the placebo group did not show any significant changes during the same time (Figure 2).

Effect of transient increase of insulin in the circulation on platelet response to prostaglandin E_1 and on plasma prostacyclin level: The effect of increased plasma levels of insulin on the minimal inhibitory concentration of PGE_1 and plasma PGI_2 in experimental group B patients could be seen within 1 hour of the hormone injection (Table I). However, the decrease in plasma PGI_2 levels was slower than the decrease in sensitivity of the platelets to the inhibitory effect of PGE_1.

Readministration of insulin in the same patients resulted in the resensitization of the platelets to the inhibitory effect of the prostaglandin and in an increase in plasma PGI_2 levels (not shown).

Clinical symptoms induced by bolus injection of insulin to patients with unstable angina pectoris and acute myocardial infarction: Administration of insulin for 7 days to these patients, as previously described, did not result in a change in blood coagulation profile. The prothrombin time, which was 15 ± 1 seconds on day 0 (n = 10), remained essentially the same (17 ± 3 seconds) on day 7. The activated partial thromboplastin time (40 ± 3 seconds) of these patients on day 0 also did not change after 7 days of insulin therapy (38 ± 5 seconds).

No patient who received insulin infusion had an increase in blood pressure, distress, restlessness, diaphoresis or nausea. Administration of insulin in patients with unstable angina pectoris and myocardial infarction did not adversely affect the plasma sodium and potassium levels, which remained within the normal ranges. Moreover, although all 20 patients in the placebo group needed analgesics, during the study period only 8 of 20 patients in experimental group A required any of these medications after insulin therapy was begun.

TABLE I Effect of Transient Increase in Plasma Insulin Level on the Inhibition of Platelet Aggregation by Prostaglandin E_1 and Plasma Prostacyclin Level in Unstable Angina Pectoris and Acute Myocardial Infarction

Time After Injection of Insulin (min)	Plasma Insulin (μU/ml)	Minimal Inhibitory Concentration of PGE_1 (nM)	Plasma PGI_2 (pM)
0	17 ± 8	66 ± 35	9 ± 3
20	176 ± 60	48 ± 7	11 ± 4
30	75 ± 16	31 ± 12	15 ± 6
60	18 ± 10	28 ± 10	16 ± 7
120	19 ± 12	68 ± 10	11 ± 5
240	17 ± 10	65 ± 12	8 ± 7

Values are mean ± SD (n = 6).
PGE_1 = prostaglandin E_1; PGI_2 = prostacyclin.

DISCUSSION

These results showed that the impaired response of platelets in unstable angina pectoris and acute myocardial infarction to prostaglandin could be "normalized" by bolus injection of physiologic amounts of insulin (equivalent to postprandial level) and thus the use of the hormone could be of therapeutic importance in the control of platelet aggregation in this condition. Repeated injection of insulin did not result in the desensitization of the hormonal effects, and the restored sensitivity of the patients' platelets to PGE_1 could be maintained indefinitely, and if necessary, by the administration of the hormone.

Because the in vivo increase in insulin stimulated the synthesis of PGI_2, the administration of the hormone would not only increase the sensitivity of platelets to prostaglandins, but it would also provide the necessary prostanoid in the milieu. Furthermore, these patients were hyperglycemic (glucose, 136 ± 26 mg/dl) with low levels of plasma insulin (17 ± 10 μU/ml), which was similar to the hormone level in fasting normal volunteers (glucose, 95 ± 10 mg/dl; n = 40). Under normal conditions, the postprandial level of glucose in the range of 136 ± 26 mg/dl would increase the insulin level to 100–150 μU/ml. As such, the administration of insulin could probably be more beneficial than the infusion of PGI_2 in this condition. Additionally, repeated injection of insulin in these patients did not produce any discernable effect on prothrombin time or partial thromboplastin time, or on blood pressure.

It has been reported earlier that the platelet PGE_1/I_2 receptor numbers, which decreased during the acute phase of the disease, returned to normal range during recovery[22–24] resulting in the increased sensitivity of these cells to the prostanoids. In the present study, we intended to control platelet aggregation in vivo through the up-regulation of putative prostaglandin receptor numbers in platelet membrane by repeated injection of insulin in these patients. The purpose was to assist the system for the subsequent increase in sensitivity of platelets to prostaglandin in the recovery phase. Although the study was terminated after 7 days of insulin administration, these results nevertheless indicated the feasibility of administering insulin for a longer period of time, if needed, for the "normalization" of platelet response to prostaglandin.

Numerous studies have used insulin in glucose-potassium solution to stimulate myocardial function. Although older studies reported an unfavorable effect of insulin in patients with myocardial infarction,[25] other studies including more recent investigations have shown a beneficial effect of the hormone during this condition.[26–30] However, these studies were performed in the absence of insulin-dependent biochemical end points related to the pathophysiology of the disease. As previously reported (Table I), the effect of bolus injection of insulin on the inhibition of platelet aggregation by PGE_1 and plasma PGI_2 levels persisted between 1 and 2 hours. Ideally, therefore, bolus injection of insulin should be administered every 2 to 3 hours in the acute phase of the condition to control platelet aggregation. In our study, we administered insulin by bolus injection every 6 hours. This schedule, although not ideal, was satis-

factory in this limited study. In contrast, in the above-mentioned multicenter study,[25] the quantity of insulin used (10 U per patient twice a day) would be too small to have any effect on platelets or plasma PGI_2 levels as a whole. Because the development of thrombosis in unstable angina pectoris and myocardial infarction is the cause rather than the effect of the ischemic condition,[6–11] it might be feasible to administer insulin in physiologic quantities as long as needed, to normalize platelet aggregation and prostaglandin response.

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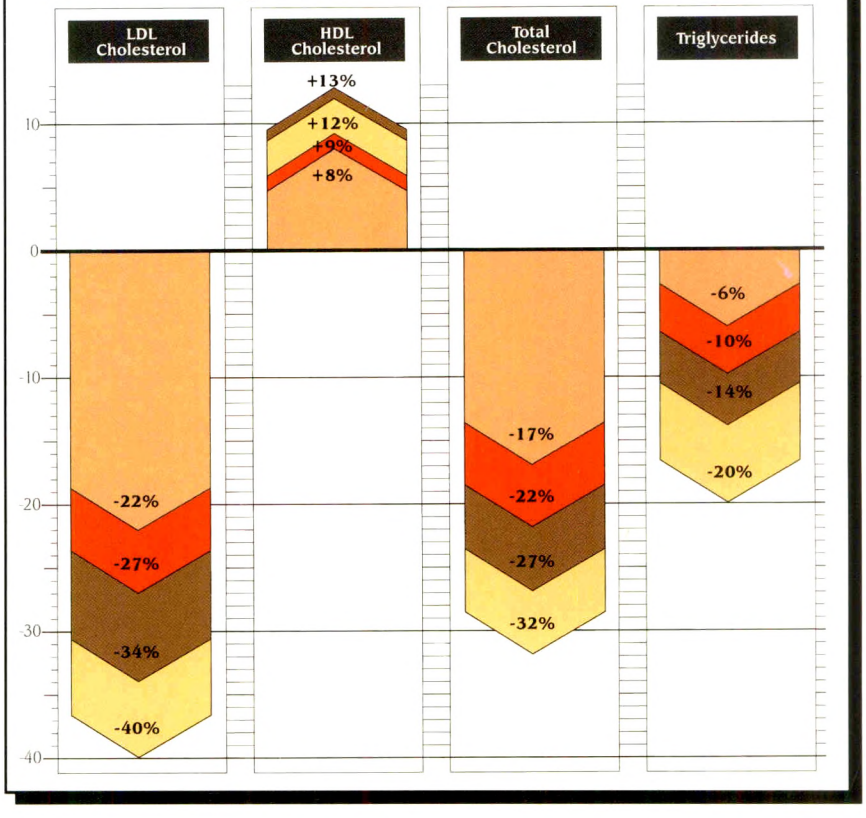
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For a wide range of patients with primary hypercholesterolemia (Types IIa and IIb), after an adequate trial of diet and other nondrug therapy,

ONCE-A-DAY ZOCOR™ (SIMVASTATIN)



ONCE-A-DAY ZOCOR™ (SIMVASTATIN)

ZOCOR is available in 5-mg, 10-mg, 20-mg, and 40-mg tablet strengths.

CONTRAINDICATIONS: Hypersensitivity to any component of this medication.

Active liver disease or unexplained persistent elevations of serum transaminases (see WARNINGS).

Pregnancy and lactation. Atherosclerosis is a chronic process, and the discontinuation of lipid-lowering drugs during pregnancy should have little impact on the outcome of long-term therapy of primary hypercholesterolemia. Moreover, cholesterol and other products of the cholesterol biosynthesis pathway are essential components for fetal development, including synthesis of steroids and cell membranes. Because of the ability of HMG-CoA reductase inhibitors such as ZOCOR® (Simvastatin) to decrease the synthesis of cholesterol and possibly other products of the cholesterol biosynthesis pathway, ZOCOR may cause fetal harm when administered to a pregnant woman. Therefore, simvastatin is contraindicated during pregnancy and in nursing mothers. **Simvastatin should be administered to women of childbearing age only when such patients are highly unlikely to conceive.** If a patient becomes pregnant while taking this drug, simvastatin should be discontinued and the patient should be apprised of the potential hazard to the fetus.

WARNINGS: ***Liver Dysfunction:*** **Persistent increases (to more than 3 times the upper limit of normal) in serum transaminases have occurred in 1% of patients who received simvastatin in clinical trials.** When drug treatment was interrupted or discontinued in these patients, the transaminase levels usually fell slowly to pretreatment levels. The increases were not associated with jaundice or other clinical signs or symptoms. There was no evidence of hypersensitivity.

It is recommended that liver function tests be performed during therapy with simvastatin. Serum transaminase levels, including ALT (SGPT), should be monitored before treatment begins, every 6 weeks for the first 3 months, every 8 weeks during the remainder of the first year, and periodically thereafter (e.g., at approximately 6-month intervals). Special attention should be paid to patients who develop elevated serum transaminase levels, and in these patients, measurements should be repeated promptly and then performed more frequently. If the transaminase levels show evidence of progression, particularly if they rise to 3 times the upper limit of normal and are persistent, the drug should be discontinued. Liver biopsy should be considered if elevations persist beyond the discontinuation of the drug.

The drug should be used with caution in patients who consume substantial quantities of alcohol and/or have a past history of liver disease. Active liver diseases or unexplained transaminase elevations are contraindications to the use of simvastatin.

As with other lipid-lowering agents, moderate (less than 3 times the upper limit of normal) elevations of serum transaminases have been reported following therapy with simvastatin. These changes appeared soon after initiation of therapy with simvastatin, were often transient, were not accompanied by any symptoms, and did not require interruption of treatment.

Skeletal Muscle: Rare cases of rhabdomyolysis with acute renal failure secondary to myoglobinuria have been associated with simvastatin therapy. Rhabdomyolysis has also been associated with other HMG-CoA reductase inhibitors when they were administered alone or concomitantly with 1) immunosuppressive therapy, including cyclosporine in cardiac transplant patients; 2) gemfibrozil or lipid-lowering doses (≥1 g/day) of nicotinic acid in non-transplant patients; or 3) erythromycin in seriously ill patients. Some of the patients who had rhabdomyolysis in association with the reductase inhibitors had preexisting renal insufficiency, usually as a consequence of longstanding diabetes. In most subjects who have had an unsatisfactory lipid response to either simvastatin or gemfibrozil alone, the possible benefits of combined therapy with these drugs are not considered to outweigh the risk of severe myopathy, rhabdomyolysis, and acute renal failure. While it is not known whether this interaction occurs with fibrates other than gemfibrozil, myopathy and rhabdomyolysis have occasionally been associated with the use of other fibrates alone, including clofibrate. Therefore, the combined use of simvastatin with other fibrates should generally be avoided.

Physicians contemplating combined therapy with simvastatin and lipid-lowering doses of nicotinic acid or with immunosuppressive drugs should carefully weigh the potential benefits and risks and should carefully monitor patients for any signs or symptoms of muscle pain, tenderness, or weakness, particularly during the initial months of therapy and during any periods of upward dosage titration of either drug. Periodic creatine phosphokinase (CPK) determinations may be considered in such situations, but there is no assurance that such monitoring will prevent the occurrence of severe myopathy.

Because of an apparent relationship between myopathy and increased plasma levels of active metabolites derived from other HMG-CoA reductase inhibitors, the daily dosage should not exceed 10 mg/day in patients who are taking cyclosporine (see DOSAGE AND ADMINISTRATION in Prescribing Information).

Simvastatin therapy should be temporarily withheld or discontinued in any patient who has an acute, serious condition suggestive of a myopathy or who has a risk factor predisposing to the development of renal failure secondary to rhabdomyolysis (e.g., severe acute infection, hypotension, major surgery, trauma, severe metabolic, endocrine, and electrolyte disorders, and uncontrolled seizures).

Myopathy should be considered in any patient with diffuse myalgias, muscle tenderness or weakness, and/or marked elevation of CPK. Patients should be advised to report promptly unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever. Simvastatin therapy should be discontinued if markedly elevated CPK levels occur or if myopathy is diagnosed or suspected.

PRECAUTIONS: ***General:*** Before instituting therapy with ZOCOR, an attempt should be made to control hypercholesterolemia with appropriate diet, exercise, and weight reduction in obese patients and to treat other underlying medical problems (see INDICATIONS AND USAGE in Prescribing Information).

Simvastatin may cause elevation of CPK and transaminase levels (see WARNINGS and ADVERSE REACTIONS). This should be considered in the differential diagnosis of chest pain in a patient on therapy with simvastatin.

Homozygous Familial Hypercholesterolemia: ZOCOR is less effective in patients with the rare homozygous familial hypercholesterolemia, possibly because these patients have few functional LDL receptors.

Information for Patients: Patients should be advised to report promptly unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever.

Drug Interactions: *Immunosuppressive Drugs, Gemfibrozil, Niacin (Nicotinic Acid), Erythromycin:* See WARNINGS, *Skeletal Muscle.*

Antipyrine: Because simvastatin had no effect on the pharmacokinetics of antipyrine, interactions with other drugs metabolized via the same cytochrome isozymes are not expected.

Propranolol: In healthy male volunteers, there was a significant decrease in mean C_{max}, but no change in AUC, for simvastatin total and active inhibitors with concomitant administration of single doses of ZOCOR® (Simvastatin) and propranolol. The clinical relevance of this finding is unclear. The pharmacokinetics of the enantiomers of propranolol were not affected.

Digoxin: Concomitant administration of a single dose of digoxin in healthy male volunteers receiving simvastatin resulted in a slight elevation (less than 0.3 ng/mL) in digoxin concentrations in plasma (as measured by a radioimmunoassay) compared to concomitant administration of placebo and digoxin. Patients taking digoxin should be monitored appropriately when simvastatin is initiated.

Warfarin: Simvastatin therapy appeared to enhance slightly the anticoagulant effect of warfarin (mean changes in prothrombin time less than 2 seconds) in normal volunteers maintained in a state of low therapeutic anticoagulation. With other reductase inhibitors, clinically evident bleeding and/or increased prothrombin time has been reported in a few patients taking coumarin anticoagulants concomitantly. In such patients, prothrombin time should be determined before starting simvastatin and frequently enough during early therapy to insure that no significant alteration of prothrombin time occurs. Once a stable prothrombin time has been documented, prothrombin times can be monitored at the intervals usually recommended for patients on coumarin anticoagulants. If the dose of simvastatin is changed, the same procedure should be repeated. Simvastatin therapy has not been associated with bleeding or with changes in prothrombin time in patients not taking anticoagulants.

Other Concomitant Therapy: Although specific interaction studies were not performed, in clinical studies, simvastatin was used concomitantly with angiotensin-converting-enzyme (ACE) inhibitors, beta blockers, calcium channel blockers, diuretics, and nonsteroidal anti-inflammatory drugs (NSAIDs) without evidence of clinically significant adverse interactions. The effect of cholestyramine on the absorption and kinetics of simvastatin has not been determined.

Endocrine Function: HMG-CoA reductase inhibitors interfere with cholesterol synthesis and as such might theoretically blunt adrenal and/or gonadal steroid production. However, clinical studies have shown that simvastatin does not reduce basal plasma cortisol concentration or impair adrenal reserve and does not reduce basal plasma testosterone concentration (see CLINICAL PHARMACOLOGY, *Clinical Studies* in Prescribing Information). Another HMG-CoA reductase inhibitor has been shown to reduce the plasma testosterone response to HCG, the effect of simvastatin on HCG-stimulated testosterone secretion has not been studied.

Results of clinical trials with drugs in this class have been inconsistent with regard to drug effects on basal and reserve steroid levels. The effects of HMG-CoA reductase inhibitors on male fertility have not been studied in adequate numbers of male patients. The effects, if any, on the pituitary-gonadal axis in pre-menopausal women are unknown. Patients treated with simvastatin who develop clinical evidence of endocrine dysfunction should be evaluated appropriately. Caution should also be exercised if an HMG-CoA reductase inhibitor or other agent used to lower cholesterol levels is administered to patients who are also receiving other drugs (e.g., ketoconazole, spironolactone, cimetidine) that may decrease the levels or activity of endogenous steroid hormones.

CNS Toxicity: Optic nerve degeneration was seen in clinically normal dogs treated with simvastatin for 14 weeks at 180 mg/kg/day, a dose that produced mean plasma drug levels about 44 times higher than the mean drug level in humans taking 40 mg/day.

CNS vascular lesions, characterized by perivascular hemorrhage and edema, mononuclear cell infiltration of perivascular spaces, perivascular fibrin deposits, and necrosis of small vessels, were seen in dogs treated with simvastatin at a dose of 360 mg/kg/day, a dose that produced plasma drug levels that were about 50 times higher than the mean drug levels in humans taking 40 mg/day. Similar CNS vascular lesions have been observed with several other drugs of this class.

A chemically similar drug in this class also produced optic nerve degeneration (Wallerian degeneration of retinogeniculate fibers) in clinically normal dogs in a dose-dependent fashion starting at 60 mg/kg/day, a dose that produced mean plasma drug levels about 30 times higher than the mean drug level in humans taking the highest recommended dose (as measured by total enzyme inhibitory activity). This same drug also produced vestibulocochlear Wallerian-like degeneration and retinal ganglion cell chromatolysis in dogs treated for 14 weeks at 180 mg/kg/day, a dose that resulted in a mean plasma drug level similar to that seen with the 60 mg/kg/day dose.

Carcinogenesis, Mutagenesis, Impairment of Fertility: In a 72-week carcinogenicity study, mice were administered daily doses of simvastatin of 25, 100, and 400 mg/kg body weight, which resulted in mean plasma drug levels approximately 3, 15, and 33 times higher than the mean human plasma drug concentration (as total inhibitory activity) after a 40-mg oral dose. Liver carcinomas were significantly increased in high-dose females and in mid- and high-dose males, with a maximum incidence of 90% in males. The incidence of adenomas of the liver was significantly increased in mid- and high-dose females. Drug treatment also significantly increased the incidence of lung adenomas in mid- and high-dose males and females. Adenomas of the Harderian gland (a gland of the eye of rodents) were significantly higher in high-dose mice than in controls. No evidence of a tumorigenic effect was observed at 25 mg/kg/day. Although mice were given up to 500 times the human dose (HD) on a mg/kg body weight basis, blood levels of HMG-CoA reductase inhibitory activity were only 3 to 33 times higher in mice than in humans given 40 mg of ZOCOR.

In a separate 92-week carcinogenicity study in mice at doses of up to 25 mg/kg/day, no evidence of a tumorigenic effect was observed. Although mice were given up to 31 times the human dose on a mg/kg basis, plasma drug levels were only 2 to 4 times higher than in humans given 40 mg simvastatin as measured by AUC.

In a 2-year study in rats, there was a statistically significant increase in the incidence of thyroid follicular adenomas in female rats exposed to approximately 45 times higher levels of simvastatin than humans given 40 mg simvastatin (as measured by AUC). Preliminary results from a second 2-year rat study indicate an increase in the incidence of thyroid and liver tumors in male and female rats at doses that produce exposure levels ≥29 times (based on AUC) those achieved in humans at a dosage of 40 mg/day. Liver tumors are found in rodents with all the chemically similar drugs of this class. No increased incidence of tumors was observed at doses that produce exposure levels 15 times (based on AUC) those seen in man.

No evidence of mutagenicity was observed in a microbial mutagen test using mutant strains of *Salmonella typhimurium* with or without rat or mouse liver metabolic activation. In addition, no evidence of damage to genetic material was noted in an *in vitro* alkaline elution assay using rat hepatocytes, a V-79 mammalian cell forward mutation study, an *in vitro* chromosome aberration study in CHO cells, or an *in vivo* chromosomal aberration assay in mouse bone marrow.

There was decreased fertility in male rats treated with simvastatin for 34 weeks at 25 mg/kg body weight (15 times the maximum human exposure level, based on AUC, in patients receiving 40 mg/day); however, this effect was not observed during a subsequent fertility study in which simvastatin was administered at this same dose level to male rats for 11 weeks (the entire cycle of spermatogenesis including epididymal maturation). No microscopic changes were observed in the testes of rats from either study. At 180 mg/kg/day (which produces exposure levels 44 times higher than those in humans taking 40 mg/day), seminiferous tubule degeneration (necrosis and loss of spermatogenic epithelium) was observed. In dogs, there was drug-related testicular atrophy, decreased spermatogenesis, spermatocytic degeneration, and giant cell formation at 10 mg/kg/day (approximately 7 times the human exposure level, based on AUC, at 40 mg/day). The clinical significance of these findings is unclear.

Pregnancy: *Pregnancy Category X.* See CONTRAINDICATIONS.

Safety in pregnant women has not been established. Simvastatin was not teratogenic in rats at doses of 25 mg/kg/day or in rabbits at doses of up to 10 mg/kg daily. These doses resulted in 6 times (rat) or 4 times (rabbit) the human exposure based on mg/m^2 surface area. However, in studies with another structurally related HMG-CoA reductase inhibitor, skeletal malformations were observed in rats and mice. Simvastatin should be administered to women of childbearing potential only when such patients are highly unlikely to conceive and have been informed of the potential hazards. If a woman becomes pregnant while taking simvastatin, it should be discontinued and the patient should be advised again as to the potential hazards to the fetus.

Nursing Mothers: It is not known whether simvastatin is excreted in human milk. Because a small amount of another drug in this class is excreted in human milk and because of the potential for serious adverse reactions in nursing infants, women taking simvastatin should not nurse their infants (see CONTRAINDICATIONS).

Pediatric Use: Safety and effectiveness in children and adolescents have not been established. Because children and adolescents are not likely to benefit from cholesterol lowering for at least a decade and because experience with this drug is limited (no studies in subjects below the age of 20 years), treatment of children or adolescents with simvastatin is not recommended at this time.

ADVERSE REACTIONS: In the controlled clinical studies and their open extensions (2,423 patients with mean duration of follow-up of approximately 18 months), 1.4% of patients were discontinued due to adverse experiences attributable to ZOCOR® (Simvastatin). Adverse reactions have usually been mild and transient. ZOCOR has been evaluated for serious adverse reactions in more than 21,000 patients and is generally well tolerated.

Clinical Adverse Experiences: Adverse experiences occurring at an incidence of 1% or greater in patients treated with ZOCOR, regardless of causality, in controlled clinical studies are shown in the table below:

	ZOCOR (N=1,583)	Placebo (N=157)	Cholestyramine (N=179)	Probucol (N=81)
Body as a Whole				
Abdominal pain	3.2%	3.2%	8.9%	2.5%
Asthenia	1.6	2.5	1.1	1.2
Gastrointestinal				
Constipation	2.3	1.3	29.1	1.2
Diarrhea	1.9	2.5	7.8	3.7
Dyspepsia	1.1	—	4.5	3.7
Flatulence	1.9	1.3	14.5	6.2
Nausea	1.3	1.9	10.1	2.5
Nervous System/Psychiatric				
Headache	3.5	5.1	4.5	3.7
Respiratory				
Upper respiratory infection	2.1	1.9	3.4	6.2

The following effects have been reported with drugs in this class:

Skeletal: Myopathy, rhabdomyolysis, arthralgias.

Neurological: Dysfunction of certain cranial nerves (including alteration of taste, impairment of extraocular movement, facial paresis), tremor, vertigo, memory loss, paresthesia, peripheral neuropathy, peripheral nerve palsy, anxiety, insomnia, depression.

Hypersensitivity Reactions: An apparent hypersensitivity syndrome has been reported rarely which has included one or more of the following features: anaphylaxis, angioedema, lupus erythematous-like syndrome, polymyalgia rheumatica, vasculitis, purpura, thrombocytopenia, leukopenia, hemolytic anemia, positive ANA, ESR increase, arthritis, arthralgia, urticaria, asthenia, photosensitivity, fever, chills, flushing, malaise, dyspnea, toxic epidermal necrolysis, erythema multiforme, including Stevens-Johnson syndrome.

Gastrointestinal: Pancreatitis; hepatitis, including chronic active hepatitis, cholestatic jaundice, fatty change in liver, and, rarely, cirrhosis, fulminant hepatic necrosis, and hepatoma; anorexia; vomiting.

Skin: Alopecia.

Reproductive: Gynecomastia, loss of libido, erectile dysfunction.

Eye: Progression of cataracts (lens opacities), ophthalmoplegia.

Laboratory Abnormalities: Elevated transaminases, alkaline phosphatase, and bilirubin; thyroid function abnormalities.

Laboratory Tests: Marked persistent increases of serum transaminases have been noted (see WARNINGS, *Liver Dysfunction*). About 5% of patients had elevations of CPK levels of 3 or more times the normal value on one or more occasions. This was attributable to the noncardiac fraction of CPK. Muscle pain or dysfunction usually was not reported (see WARNINGS, *Skeletal Muscle*).

Concomitant Therapy: In controlled clinical studies in which simvastatin was administered concomitantly with cholestyramine, no adverse reactions peculiar to this concomitant treatment were observed. The adverse reactions that occurred were limited to those reported previously with simvastatin or cholestyramine. The combined use of simvastatin with fibrates should generally be avoided (see WARNINGS, *Skeletal Muscle*).

OVERDOSAGE: Significant lethality was observed in mice after a single oral dose of 9 g/m^2. No evidence of lethality was observed in rats or dogs treated with doses of 30 and 100 g/m^2, respectively. No specific diagnostic signs were observed in rodents. At these doses, the only signs seen in dogs were emesis and mucoid stools.

There have been no cases of clinically significant overdosage with ZOCOR in humans. Until further experience is obtained, no specific treatment of overdosage with ZOCOR can be recommended.

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J2Z007R(902)

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Acute Conversion of Paroxysmal Supraventricular Tachycardia with Intravenous Diltiazem

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Diltiazem has electrophysiologic effects similar to those of verapamil. Its efficacy and safety in 4 doses for treatment of induced supraventricular tachycardia (SVT) were examined and compared with those of placebo in 87 patients (25 with atrioventricular [AV] nodal reentry tachycardia, 60 with AV reentry associated with an accessory AV connection, and 2 with atrial tachycardia). Conversion to sinus rhythm occurred in 4 of 14 patients (29%) with 0.05 mg/kg of diltiazem, 16 of 19 (84%) with 0.15 mg/kg, 13 of 13 (100%) with 0.25 mg/kg, and 14 of 17 (82%) with 0.45 mg/kg compared with 6 of 24 (25%) treated with placebo. Conversion rates in groups receiving doses of 0.15 to 0.45 mg/kg of diltiazem were superior to that in the placebo group ($p < 0.001$). Time to conversion was 3.0 ± 2.6 minutes in responding diltiazem patients compared with 5.9 ± 6.1 minutes in responding control patients. Diltiazem administration resulted in significant lengthening of SVT cycle length, AH interval, and AV nodal effective refractory period and block cycle length. The most frequent adverse response to diltiazem was hypotension (7 of 63 patients); however, only 4 patients had symptoms related to hypotension. Thus, intravenous diltiazem in doses of 0.15, 0.25 and 0.45 mg/kg is an effective and safe treatment for the acute management of SVT.

(Am J Cardiol 1992;70:587–592)

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Acute termination of paroxysmal supraventricular tachycardia (SVT) is usually achieved by interrupting reciprocation at the level of the atrioventricular (AV) node. The usefulness of intravenous verapamil and adenosine for this purpose is well-recognized, achieving successful conversion to sinus rhythm in >80% of cases.[1–7] However, because of verapamil's negative inotropic and vasodilator effects, profound hypotension and even cardiac arrest may occasionally complicate its use.[8–12] Diltiazem is a calcium antagonist with electrophysiologic effects similar to those of verapamil, but with minimal negative inotropic potential and possibly less hypotensive effect.[11,13–19] It has been used intravenously to convert SVT to sinus rhythm, with an overall efficacy of 90% in varying doses and schedules.[20] This multicenter, randomized, double-blinded, placebo-controlled, dose-ranging study was performed to determine the safety and efficacy of intravenous diltiazem for the acute conversion of induced SVT in the setting of diagnostic electrophysiologic testing.

METHODS

Study patients: In all, 170 patients with clinical history of paroxysmal SVT were screened for eligibility; 87 entered and completed the study. Inclusion required induction of SVT with programmed stimulation during formal electrophysiologic testing. Eligible SVT was required to have a rate of ≥120 beats/min and to persist for ≥15 minutes. Patients with severe congestive heart failure, sinus node dysfunction, pregnancy, myocardial infarction within 2 weeks of study, or hypotension (systolic pressure <90 mm Hg) were excluded from the study.

Study design: The study was designed in a randomized, double-blinded, parallel format to evaluate the safety and efficacy of 4 intravenous doses of diltiazem hydrochloride compared with placebo for acute termination of induced SVT. Investigators were unaware of the study drug, but not of the dose; subjects were unaware of both, as well as of the time of drug administration.

Written informed consent was obtained from all patients. Invasive electrophysiologic testing was then performed by methods previously described.[4] Baseline spontaneous intervals and sinus node recovery times were assessed, as well as anterograde and retrograde AV node and accessory pathway refractory periods, and shortest cycle lengths maintaining 1:1 AV nodal conduction. SVT was then induced and allowed to persist without intervention for 15 minutes to confirm constancy of the arrhythmia.

Patients were then randomized to receive 1 of 4 doses of diltiazem (0.05, 0.15, 0.25 or 0.45 mg/kg) or placebo. The study drug was administered as an intravenous bolus over 2 minutes without the patient's knowledge of the timing of dose administration. The subject was then observed for response for 15 minutes after completion of the infusion. Conversion to normal sinus rhythm was considered a successful therapeutic response. Blood pressure measurement and electrocardiogram recordings were obtained at 2, 7, 12 and 17 minutes from the beginning of the infusion. SVT was terminated by programmed stimulation if conversion did not occur within 17 minutes after onset of infusion. The electrophysiologic measurements were then repeated.

Statistical analysis: Dose-response relations were examined with logistic regression methods for a dichotomous response. Mantel-Haenszel methods were used to compare response between placebo and each of the 4 diltiazem doses and between diltiazem dose groups. A separate subanalysis was performed for patients who had not received potentially interacting drugs within the previous 5 drug half-lives for the respective agents.

Rank regression procedures were used to evaluate the dose-response relation for each electrophysiologic variable, both control and after treatment. Pairwise comparisons between placebo and each diltiazem dose and between diltiazem doses were conducted on the ranks of the analysis variables. The type of SVT and the use of concomitant medications were each considered as covariables for each analysis. Exploratory covariate analysis was used to determine whether the patient characteristics affected the dose-response relation. Descriptive statistics are described as mean ± SD. Analysis of time to conversion to sinus rhythm and changes in blood pressure are calculated relative to the onset of study drug administration at time 0. Diltiazem groups were compared with placebo groups by analysis of variance.

RESULTS

Clinical characteristics of patients: Of 87 subjects (42 men and 45 women) with inducible SVT, 25 were shown to have AV nodal reentrant tachycardia, 60 AV reentrant tachycardia associated with an accessory AV connection (23 overt, 36 concealed and 1 atriofascicular) and 2 atrial tachycardia. Demographic analysis of age, sex, race and weight was not significantly different between placebo- and diltiazem-treated subjects. Historical frequency of SVT episodes before entry in the study ranged from 1 episode to daily episodes and was not significantly different for the treatment groups.

Of the 87 subjects, 29 had received cardioactive drugs that had not been discontinued ≥5 drug half-lives before receiving the study drug; of these, 11 had received digoxin, 4 verapamil, 7 isoproterenol, 3 flecainide, 3 atropine, 1 nifedipine, 1 quinidine, 1 amitriptyline, 1 procainamide and 1 amiodarone. Interactive analysis of potentially interacting agents by study dose group was not significant.

The average dose of diltiazem administered for the 0.05 mg/kg group was 4.02 ± 0.68 mg (n = 14). In the 0.15 mg/kg diltiazem group, the mean dose was 11.24 ± 2.31 mg (n = 19). A mean of 16.23 ± 4.83 mg of diltiazem was administered to the 0.25 mg/kg group (n = 13) and 34.09 ± 7.04 mg to the 0.45 mg/kg group (n = 17).

Efficacy: Overall efficacy, defined as termination of SVT within 17 minutes of the onset of infusion, was 47 of 63 subjects (75%) for the 4 diltiazem groups combined compared with 6 of 24 placebo-treated patients (25%). Conversion rates showed a dose-response relation ($p < 0.001$; Figure 1). Diltiazem doses of 0.15, 0.25 and 0.45 mg/kg were all effective compared with placebo ($p < 0.001$). Efficacy was not significantly different for the 0.05 mg/kg and placebo groups. The largest proportion of responders (100%) was observed in the 0.25 mg/kg dose, but was not statistically different from that in the other 2 effective doses. When the 29

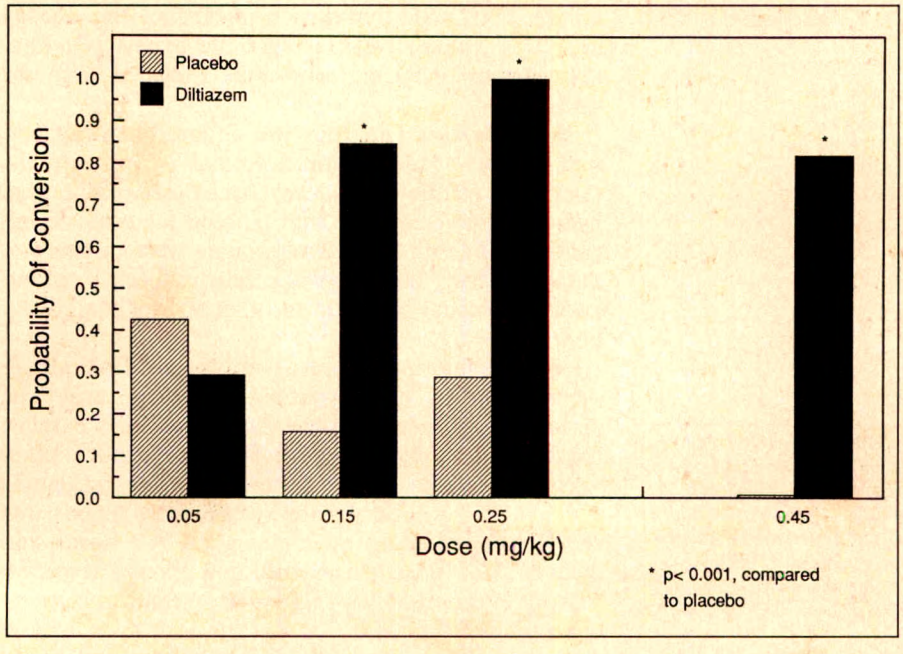


FIGURE 1. Probability of termination of supraventricular tachycardia. Each diltiazem group is compared with its control group. Dose trend ($p < 0.001$) is demonstrated. Doses of 0.15, 0.25 and 0.45 mg/kg were each effective.

patients who had received concomitant cardioactive medication (which may potentially have affected response) were excluded, the efficacy rates were not significantly changed, again showing a significant dose trend ($p < 0.001$). There was no significant difference in the dose-response relation found by individual investigators.

Subgroup analysis showed no difference in the dose-response relation based on mechanism of SVT (AV nodal reentry vs AV reentry; Table I). The 1 patient with AV reentry using an atriofascicular fiber received placebo and did not respond. Of the 2 subjects with atrial tachycardia, 1 received 0.15 mg/kg of diltiazem and SVT terminated 1 minute and 5 seconds after the onset of infusion; the other subject developed 4:1 AV block with persistent atrial tachycardia 16 minutes after receiving 0.45 mg/kg of diltiazem and then converted to a junctional rhythm 14 minutes later. Therapeutic response was not significantly different for older patients (age >60 years), faster tachycardias (SVT rate ≥185 beats/min), larger subjects (weight >75 kg) or baseline AV nodal conduction capability as measured by shortest atrial pacing cycle length maintaining 1:1 AV nodal conduction.

The time from onset of diltiazem infusion to conversion to sinus rhythm in responders is shown in Figure 2. Overall response time in diltiazem-treated patients was 3.0 ± 2.6 minutes compared with 5.9 ± 6.1 minutes in the control group. Response times in the placebo and 0.05 mg/kg groups were longer than those in the 3 higher dose groups; however, only the 0.45 mg/kg group responded in a significantly shorter time than did the placebo-treated group ($p \leq 0.05$).

Electrophysiologic effects: Figure 3 illustrates the electrophysiologic effects of diltiazem infusion. Significant linear dose trends were observed in SVT cycle length, AH interval during sinus rhythm and SVT, shortest atrial pacing cycle length maintaining 1:1 AV nodal conduction, and AV nodal effective refractory period, each of which increased in response to diltiazem ($p < 0.01$). No significant trend was observed in QRS duration, QT interval, maximal corrected sinus node recovery time, HV interval, VA intervals, atrial effective or functional refractory periods, ventricular effective or functional refractory periods, or in shortest atrial pacing cycle lengths maintaining 1:1 accessory AV connection conduction or accessory AV connection refractory periods (anterograde or retrograde).

TABLE I Response to Diltiazem: Mechanism of Supraventricular Tachycardia

	AVRT	AVNRT
Placebo	5/17	1/7
0.05 mg/kg	3/9	1/5
0.15 mg/kg	10/12	5/6
0.25 mg/kg	10/10	3/3
0.45 mg/kg	10/12	4/4

AVNRT = atrioventricular nodal reentry tachycardia; AVRT = atrioventricular reentry tachycardia.

Safety: Systolic and diastolic blood pressures were averaged over minutes 2, 7, 12 and 17 after onset of treatment and compared with those measurements at the end of baseline (immediately before infusion). There was no relation between dose of diltiazem and mean systolic blood pressure change; however, a linear dose trend was demonstrated in reduction of diastolic blood pressure ($p = 0.03$). This trend was dominated by changes in the 0.45 mg/kg group, in which mean diastolic blood pressure decreased by 12 ± 3%. In the placebo and 0.05 mg/kg groups, the reduction in diastolic blood pressure was greater in responders than in nonresponders, but in the 0.45 mg/kg group, diastolic blood pressure reduction was greater in nonresponders. There was no relation between changes in systolic blood pressure and response status.

Adverse effects of study drug administration are listed in Table II; events included are those whose relation to the study drug was thought by the investigators to be definite, probable or possible. Adverse events attributable to the electrophysiologic procedure itself, rather than to drug administration, were excluded. Of patients receiving diltiazem, 12 of 63 (19%) had ≥1 adverse event related to treatment compared with 1 of 24 pa-

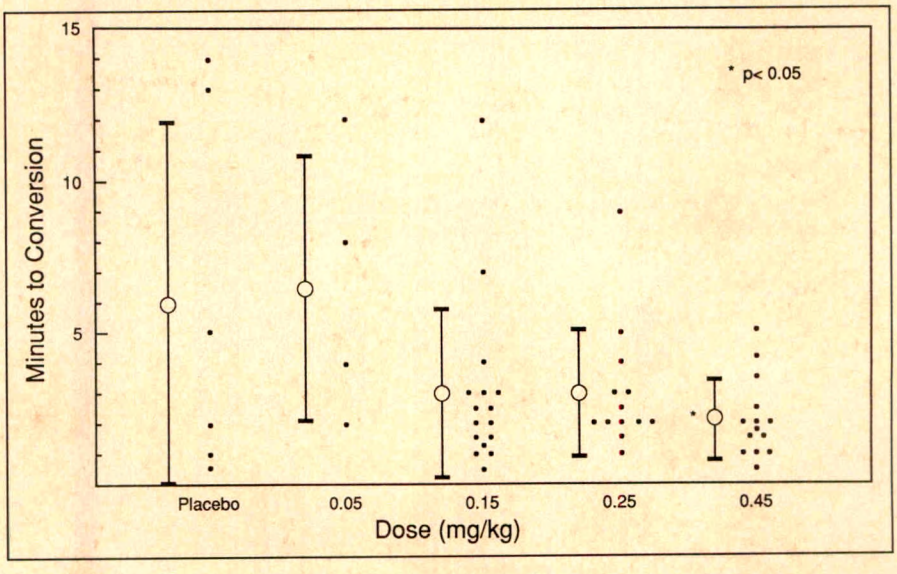


FIGURE 2. Time to response from onset of study drug infusion in individual responders.

TABLE II Adverse Effects

	Placebo	Diltiazem
General		
Paresthesias	0	1 (1.6%)
Injection site reaction	0	1 (1.6%)
Diaphoresis	0	1 (1.6%)
Cardiovascular		
Hypotension	0	7 (11.1%)
Ventricular arrhythmias	0	2 (3.2%)
Supraventricular arrhythmias	1 (4.2%)	1 (1.6%)
Syncope	0	1 (1.6%)
Flushing	0	1 (1.6%)
1° AV block	0	1 (1.6%)
2° AV block	0	1 (1.6%)

AV = atrioventricular.

tients (4%) receiving placebo (Figure 4). Although adverse effects occurred more frequently in higher dose groups, differences between groups were not statistically significant.

The most frequent adverse event was hypotension (systolic blood pressure <90 mm Hg), occurring in 10 of 63 patients (16%) receiving diltiazem. No patient receiving either 0.05 mg/kg of diltiazem or placebo had hypotension. Symptoms accompanied hypotension in 7 of the 10 patients and needed intervention in 6 (intravenous fluids, Trendelenberg positioning, atropine or calcium chloride, or a combination). In 4 patients needing intervention, hypotension was not thought by the investigator to be related to the drug, but rather to a vasodepressor reaction to catheter removal (n = 3) or to the

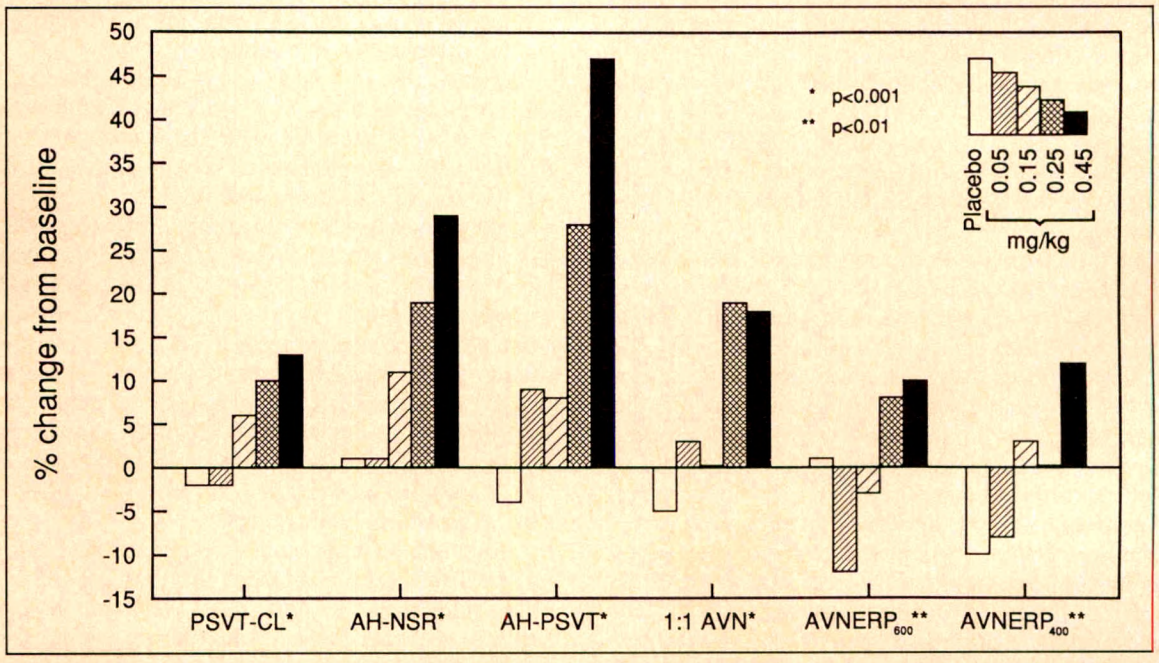


FIGURE 3. Electrophysiologic effects of intravenous diltiazem, described in percent change from baseline at −15 minutes to after infusion at 17 minutes. AH-NSR = AH interval in sinus rhythm; AH-PSVT = AH interval in supraventricular tachycardia; 1:1 AVN = shortest paced atrial cycle length maintaining 1:1 atrioventricular conduction; $AVNERP_{400}$ = atrioventricular nodal effective refractory period at drive cycle length of 400 ms; $AVNERP_{600}$ = atrioventricular nodal effective refractory period at drive cycle length of 600 seconds; PSVT-CL = supraventricular tachycardia cycle length.

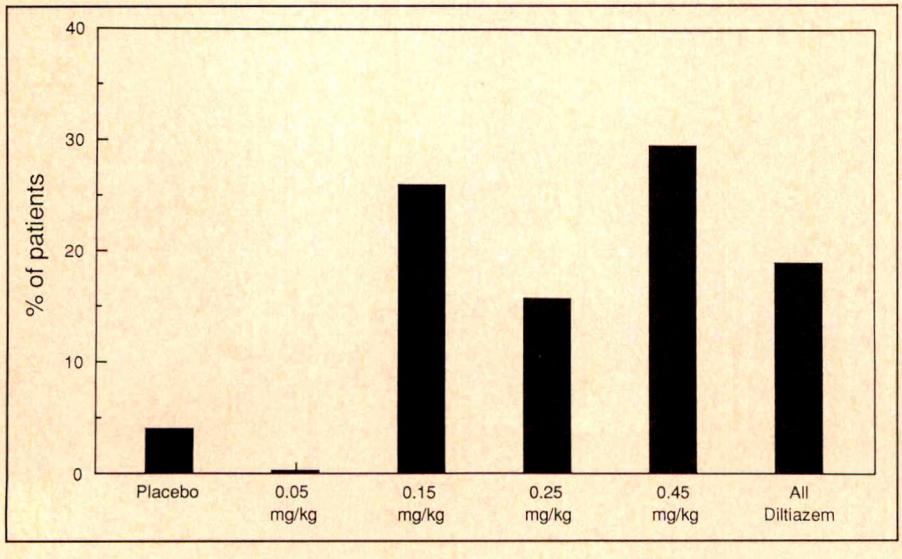


FIGURE 4. Incidence of adverse effects related to treatment.

abruptness of the termination of SVT (n = 1). Thus, hypotension related to diltiazem occurred in only 7 of 63 patients (11%). Hypotension occurred at a mean of 14.3 minutes (range 2 to 47) after onset of drug infusion and lasted a mean of 21 minutes (range 1 to 60).

New arrhythmias thought to be related to study drug administration were observed in 4 diltiazem and 1 placebo patient after treatment. One subject (a nonresponder to 0.45 mg/kg of diltiazem with atrial tachycardia who was previously described) developed 4:1 AV nodal conduction 16 minutes after drug administration with persistent atrial tachycardia, resulting in a ventricular rate of 60 beats/min. Conversion to a junctional rhythm with hypotension (57/38 mm Hg) occurred 14 minutes later and needed intravenous fluid administration and Trendelenberg positioning. Other new arrhythmias observed included 1° AV block and nonsustained ventricular tachycardia. One subject (who had earlier needed isoproterenol to induce SVT) converted to sinus rhythm with a 4-beat run of ventricular tachycardia 5 minutes after diltiazem administration. During programmed stimulation of the right ventricle 23 minutes later, ventricular fibrillation was induced, needing defibrillation. The investigator thought that these arrhythmias were probably related to isoproterenol effect rather than to diltiazem effect.

DISCUSSION

This study demonstrates that intravenous diltiazem is effective in terminating paroxysmal SVT. The response is dose-dependent, as demonstrated by the dose trend shown in Figure 1. Doses of 0.15, 0.25 and 0.45 mg/kg were each effective, although the maximal response was noted in the 0.25 mg/kg group (100%).

The moment of arrhythmia termination was actually recorded in very few patients; thus, the site of conduction block could not be specifically analyzed. Because diltiazem produced significant dose-dependent depression of AV nodal conduction and prolongation of AV nodal refractoriness, with no significant effect on either retrograde AV nodal parameters or accessory pathway conduction or refractoriness, it is likely that diltiazem's therapeutic effect was related to its action at the AV node (specifically, at the anterograde limb of the SVT circuit).

The number of patients (n = 2) with atrial tachycardia studied was too small to obtain any conclusions regarding efficacy. One of the 2 patients experienced prompt termination of the arrhythmia with diltiazem; however, the other developed 4:1 AV block with persistent atrial tachycardia. This rate modulation would be an expected response to a drug whose primary site of action is the AV node, but which has little appreciable effect on atrial properties.

The double-blinded, placebo-controlled format of this study has particular merit in testing acute conversion of SVT. As can be seen by the number of responders to placebo (6 of 24), spontaneous termination of SVT without intervention may occur. The SVT persistence phase of 15 minutes before drug administration was intended to reduce the incidence of spontaneous conversion in the study population. Because patients were unaware of the timing of drug administration, the reduction of time to response in diltiazem-treated patients compared with placebo-treated ones is particularly significant. The time to response to placebo approximates the expected time course of spontaneous conversion.

The most frequent adverse effect of intravenous diltiazem was hypotension; however, this was associated with symptoms in very few subjects. It was difficult to specifically discern whether hypotension was caused by the drug, the prolonged arrhythmia or the electrophysiologic procedure itself in many subjects. All subjects with symptomatic hypotension were in the higher diltiazem dose groups and most were responders, suggesting that dose-related drug effect contributes to the phenomenon.

Comparison of the efficacy and adverse effect rates suggests that the optimum dose of intravenous diltiazem is 0.25 mg/kg. The data on acute termination of arrhythmias should not be directly extrapolated to efficacy of the oral drug for chronic suppression of arrhythmias. Hung et al[18] used 0.25 mg/kg of diltiazem intravenously in 30 patients with induced AV nodal reentrant tachycardia and orthodromic AV reentrant tachycardia. SVT was terminated within 1 minute in 24 of 30 subjects, most with conduction block in the anterograde limb. The response to intravenous drug administration in Hung's series was useful in predicting suppression of SVT induction by oral diltiazem and chronic suppression of clinical SVT with long-term follow-up.

APPENDIX

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Lack of Effect of Midazolam on Inducibility of Arrhythmias at Electrophysiologic Study

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Midazolam has several advantages over diazepam as a sedative agent in electrophysiologic studies, but its electrophysiologic effects in humans are unknown. Therefore, its effects were studied in 20 patients undergoing electrophysiologic studies. Electrophysiologic variables were measured before and after administration of intravenous midazolam (5 mg). There were no significant changes in the electrophysiologic variables, apart from a minor decrease in sinus cycle length (711 ± 124 vs 647 ± 91 ms; p = 0.005). Ease of inducibility of reentrant tachycardia was not significantly altered by midazolam, and tachycardia remained inducible in all patients. The drug was well-tolerated with no significant side effects, apart from a minor reduction (mean 18 mm Hg) in blood pressure (p <0.001). Good amnesic effect was achieved in 16 patients, and most patients preferred it to oral diazepam for sedation during the procedure. It is concluded that midazolam can be used safely in patients undergoing electrophysiologic studies without significantly interfering with electrophysiologic variables or the inducibility of reentrant tachycardias.

(Am J Cardiol 1992;70:593–597)

Electrophysiologic studies have been increasingly used for the study of cardiac arrhythmias. Detailed, lengthy, preoperative studies (including mapping) are vital for the management of arrhythmias, especially if surgery or catheter ablation is contemplated.[1,2] These studies are often prolonged and cause major discomfort in ≥20% of patients. Catheter ablation procedures for tachycardias are often more prolonged[3] than are standard electrophysiologic studies and produce similar or greater degrees of discomfort. Various sedative regimens are used during these studies, whose electrophysiologic effects are unknown. When repeat electrophysiologic studies are needed, some patients find the mere thought of a further study extremely unpleasant based on their experience at the first study. A safe drug that would provide sedation and amnesia with minimal electrophysiologic effects, and permit patient cooperation would help or remove many of the aforementioned problems.

Midazolam, a recently developed short-acting benzodiazepine, has been widely used for endoscopic or short surgical procedures[4,5] and more recently for radiofrequency catheter ablation procedures.[3] It has several advantages compared with diazepam including more rapid onset of action,[4,5] shorter half-life[4,6] and better anterograde amnesia after the procedure.[5,7] It has relatively mild cardiovascular and respiratory effects, and is generally well-tolerated in moderate doses.[6] However, the cardiac electrophysiologic effects of midazolam have not been studied. Therefore, we examined the effects of midazolam on human cardiac electrophysiology and the ease of induction of reentrant cardiac arrhythmias. Furthermore, its tolerability, and sedative and amnesic effects were also assessed.

METHODS

Patients: Twenty-three patients (12 men and 11 women, age range 15 to 73 years) were studied. The first 20 patients had full electrophysiologic assessment. The effect of midazolam on inducibility of tachycardia was studied in 15 of these patients. Written informed consent to this study was obtained from all patients. The Westmead Hospital research and ethics committee approved this project on June 28, 1991.

Study design: Patients fasted for ≥6 hours before the study. Valium (10 mg orally) was administered as premedication 1 hour before the procedure. All antiarrhythmic medications were stopped for ≥1 week before testing. Electrophysiologic study was performed using methods described previously.[8,9] Signals were filtered with a bandpass of 50 to 1,000 Hz. Recordings were

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TABLE I Electrophysiologic Variables Before and After Midazolam

	No. of Pts.	Before (ms)	After (ms)	p Value
SCL	20	711 ± 124	647 ± 91	0.005
PA	20	52 ± 10	51 ± 10	0.89 (NS)
AH	20	65 ± 17	64 ± 18	0.30 (NS)
HV	20	42 ± 21	42 ± 19	0.94 (NS)
QRS	20	92 ± 24	89 ± 22	0.15 (NS)
RAERP	20	207 ± 33	204 ± 28	0.40 (NS)
AVNERP	8	286 ± 64	266 ± 45	0.09 (NS)
AVNFRP	16	397 ± 62	384 ± 47	0.12 (NS)
AVW	20	315 ± 57	320 ± 59	0.26 (NS)
VAW	17	286 ± 35	295 ± 37	0.16 (NS)
RVERP	20	222 ± 15	221 ± 14	0.60 (NS)
SNRT	19	1,023 ± 286	938 ± 235	0.10 (NS)
SACT	20	111 ± 87	137 ± 151	0.39 (NS)
BP(t) (mm Hg)	20	109 ± 15	91 ± 15	<0.001
BP(e) (mm Hg)	20	109 ± 15	100 ± 13	0.002
HR (beats/min)	20	88 ± 15	100 ± 18	<0.001

AVNERP = atrioventricular node effective refractory period; AVNFRP = atrioventricular node functional refractory period; AVW = atrioventricular Wenckebach cycle length; BP(e) = blood pressure end (comparison of mean before midazolam with that immediately after completion of study); BP(t) = blood pressure trough (comparison of mean before midazolam with maximum reduction in mean after midazolam); HR = heart rate; NS = not significant; RAERP = right atrial effective refractory period; RVERP = right ventricular effective refractory period; SACT = sinoatrial conduction time; SCL = sinus cycle length; SNRT = sinus node recovery time; VAW = ventriculoatrial Wenckebach cycle length.

obtained using an 8-channel ink-jet recorder (Siemens-Elma Mingograph) at paper speeds of 100 and 250 mm/s. Atrial and ventricular pacing were performed using a battery powered stimulator (World Precision Instruments Model 870) programmed to deliver pulses of 2 ms duration at twice diastolic threshold. Anterograde atrioventricular (AV) node conduction was assessed by extrastimulus testing, using a basic cycle length as close as possible to 600 ms. The coupling intervals of atrial extrastimuli were shortened in 20 ms decrements until atrial refractoriness. Retrograde ventriculoatrial (VA) conduction was assessed in an analogous manner, using ventricular stimulation. The refractory periods of the right atrium and ventricle, and the AV conduction system were determined using the extrastimulus technique. Atrial and ventricular refractory periods were measured to the nearest 10 ms. Anterograde and retrograde conduction was also assessed by incremental pacing of the atria or ventricles until conduction block was noted. The Wenckebach cycle length was defined as the longest cycle length at which second-degree AV or VA block occurred (determined to the nearest 10 ms). Furthermore, the refractory periods of any accessory pathways were measured in both the anterograde and retrograde directions (as appropriate) in each case.

Sinus node function was assessed by sinus node recovery times and sinoatrial conduction times. In assessing sinus node recovery, the initial sinus pause and subsequent 8 sinus cycles were measured after pacing for 30 seconds at each of 3 or 4 of the following cycle lengths: 600, 500, 430 and 370 ms. Sinus node recovery time was defined as the maximal sinus pause occurring after pacing at any cycle length. Sinoatrial conduction time was estimated by Narula's method.[10] When the standard clinical study (including mapping) was completed, a 5-minute rest period was allowed for stablization of autonomic tone before repeat anterograde and retrograde AV conduction and sinus node function were assessed before administration of midazolam. In those patients in whom isoproterenol had been needed for tachycardia initiation, the sinus cycle length was allowed to return to its pre-infusion level (indicating that the effects of isoproterenol had worn off) before the aforementioned measurements were obtained at the pre-midazolam study. The following variables were measured: atrial and ventricular stimulation thresholds, baseline AV conduction intervals (including sinus cycle length, PA, AH, HV and QRS intervals), atrial effective refractory period, AV node effective and functional refractory period, ventricular refractory period, VA conduction system effective refractory period, accessory pathway refractory period (if indicated), AV and VA Wenckebach thresholds, sinus node recovery and sinoatrial conduction times, and systolic, diastolic and mean blood pressure.

Midazolam (5 mg) was then administered intravenously over 2 minutes, and after an interval of 3 minutes, repeat measurements of the aforementioned electrophysiologic variables were obtained. Identical drive cycle lengths were used before and after midazolam to avoid changes in excitability and refractoriness due to variations in heart rate. In patients with sustained reentrant tachycardia inducible during the clinical study, the ability to reinduce tachycardia was assessed after midazolam. Systolic, diastolic and mean blood pressure, and heart rate were recorded every 5 minutes after completion of midazolam injection (using the automated cuff method), and more frequently if indicated. Each patient was closely observed for any respiratory depression. All patients were questioned regarding any symptoms during or after intravenous midazolam, and their experience was compared with the sedative effects of 10 mg of oral diazepam. In a further 3 patients (nos. 21 to 23), the effect of midazolam on inducibility of tachycardia was tested without full assessment of other electrophysiologic parameters. These patients had undergone a prolonged clinical evaluation, and we thought that it would cause excessive prolongation of the case to complete the entire research study.

Values were expressed as mean ± 1 SD. Statistical analysis was performed using Student's *t* test for paired data. A p value ≤0.05 was considered significant.

RESULTS

The electrophysiologic data obtained before and after midazolam are summarized in Table I.

Atrial and ventricular stimulation thresholds were unchanged in all patients after midazolam. Analysis of baseline conduction intervals showed that sinus cycle lengths were significantly but mildly decreased after intravenous midazolam (711 ± 124 vs 647 ± 91 ms; p = 0.005) at 5 minutes, but the other conduction intervals (including PA, AH, HV and QRS) were not significantly altered (p >0.1).

Atrial effective refractory periods were not altered significantly after midazolam (p = 0.4). AV node functional refractory period was measurable in 16 patients.

The remaining 4 patients had anterograde preexcitation precluding its estimation. Midazolam caused no significant change in AV node functional refractory period ($p = 0.12$).

AV node effective refractory period was measurable in only 8 patients. In the remaining 12 patients, atrial refractoriness precluded this measurement. AV node effective refractory period was mildly shortened after midazolam, but did not reach statistical significance ($p = 0.09$). AV Wenckebach threshold was measured in all 20 patients and was not changed after midazolam ($p = 0.26$).

Ventricular effective refractory period was measured in all 20 patients and was not changed after midazolam ($p = 0.61$). VA conduction system effective refractory period was measurable in only 4 patients. In the remaining 16 patients, VA conduction was limited by ventricular refractoriness. VA Wenckebach threshold was measurable in 17 patients (the remaining 3 had VA dissociation) and was not significantly altered by midazolam ($p = 0.16$).

Sinus node recovery time was measured in 19 patients. One patient was excluded because of excessive supraventricular tachycardia induction with atrial pacing. The longest pause after pacing at the 4 different cycle lengths tested was not altered significantly ($p = 0.1$). No significant changes occurred in sinoatrial conduction time after midazolam ($p = 0.39$).

Midazolam caused a modest reduction in mean blood pressure (109 ± 15 vs 91 ± 15 mm Hg; $p < 0.001$) compared with at baseline. The lowest blood pressure was usually recorded within 15 minutes of the injection, with later blood pressures tending toward the baseline reading. Heart rate showed a corresponding mild increase after midazolam (Figures 1 and 2). A significant reduction in respiratory rate (defined as ≥25% reduction of respiratory rate/min) was observed in only 2 patients. In these patients, the suppression was very transient and improved spontaneously without active intervention. Pulse oximetry was not routinely used.

Accessory pathways and dual atrioventricular junctional pathways: The effects of midazolam on accessory pathways were studied in 6 patients (Table II). No consistent changes were seen. The effect of midazolam on dual AV junctional pathways is shown in Table III. Values were unchanged or mildly shortened.

Inducibility of reentrant arrhythmias: In all, 15 patients were tested: 6 had AV junctional reentry tachycardia, 6 had accessory pathways (including 2 concealed), 1 had intraatrial reentry tachycardia, and 2 had ventricular tachycardia associated with coronary artery disease. Ten patients needed isoproterenol for the initiation of tachycardia (AV junctional reentry tachycardia [n = 5], accessory pathways [n = 4], and intraatrial reentry tachycardia [n = 1]). In all cases, tachycardia was easily induced after midazolam. In 2 patients who needed isoproterenol for tachycardia induction at baseline, isoproterenol was not needed after midazolam.

Perceptions after midazolam: All 23 patients had a favorable response to intravenous midazolam and preferred it as a sedative to oral diazepam. The most frequent reaction was a pleasant and relaxing sensation, and 16 of 20 patients were drowsy or asleep soon after the injection was completed, although all were easily

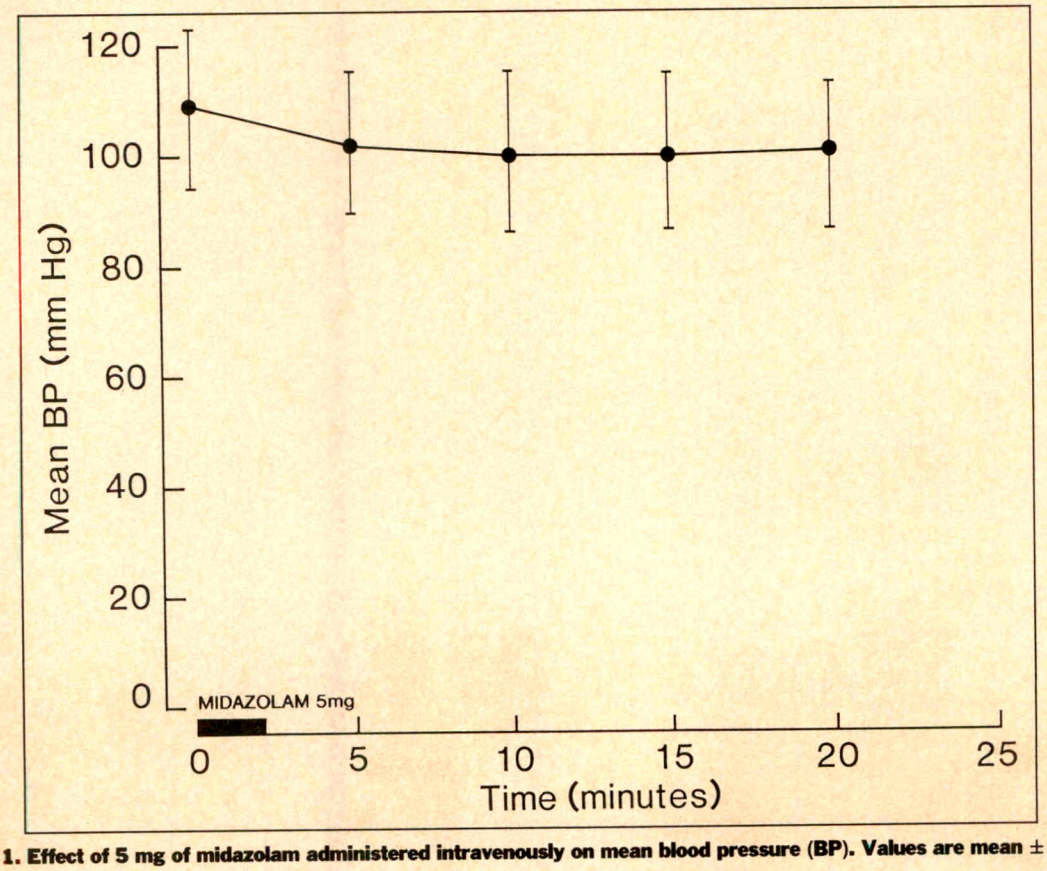


FIGURE 1. Effect of 5 mg of midazolam administered intravenously on mean blood pressure (BP). Values are mean ± SD.

awakened. Major amnesia was observed in 16 patients who when questioned several hours after the procedure noticed a memory gap soon after the injection of midazolam, with the events before injection still clear. Seventeen patients welcomed the idea of receiving midazolam again should a repeat electrophysiologic study be necessary. The remaining 3 patients had no strong preference. No patient found midazolam unpleasant or complained of any side effect. Drowsiness after the procedure was absent in all patients 5 minutes after completion of the study. Presyncopal symptoms were not observed in any patient.

DISCUSSION

The cardiovascular effects of midazolam were previously studied.[11,12] Like diazepam, it produces a mild reduction in blood pressure by a reduction in systemic vascular resistance and myocardial contractility,[13] and an increase in heart rate mediated by an intact sympathetic reflex and release of endogenous catecholamines. However, midazolam produces a greater decrease in blood pressure and slightly greater decrease in systemic vascular resistance than does diazepam.[14]

Effect on human cardiac electrophysiology: The results show that the electrophysiologic effects of midazo-

TABLE II Effect of Midazolam on Patients with Wolff-Parkinson-White Syndrome or Concealed Accessory Pathways

	SVT CL (ms)		AAVC ERP (ms)		AVAC ERP (ms)		Isoproterenol Needed for SVT Induction	
Pt. No.	C	M	C	M	C	M	C	M
4*	—	—	<180	<190	280	260	—	—
9†	450	460	—	—	<240	280	+	o
11	270	376	340	320	<250	<250	+	o
12	380	360	<270	<260	240	280	o	o
14	280	360	270	<210	<270	<260	+	+
20†	400	360	—	—	240	240	o	o

*No sustained SVT inducible.
†Concealed accessory pathway.
AAVC = accessory atrioventricular connection; AVAC = accessory ventriculoatrial connection; C = control; CL = cycle length; ERP = effective refractory period; M = midazolam; SVT = supraventricular tachycardia; + = yes; o = no; — = not present; < = respective accessory pathway ERP is less than atrial or ventricular functional refractory period.

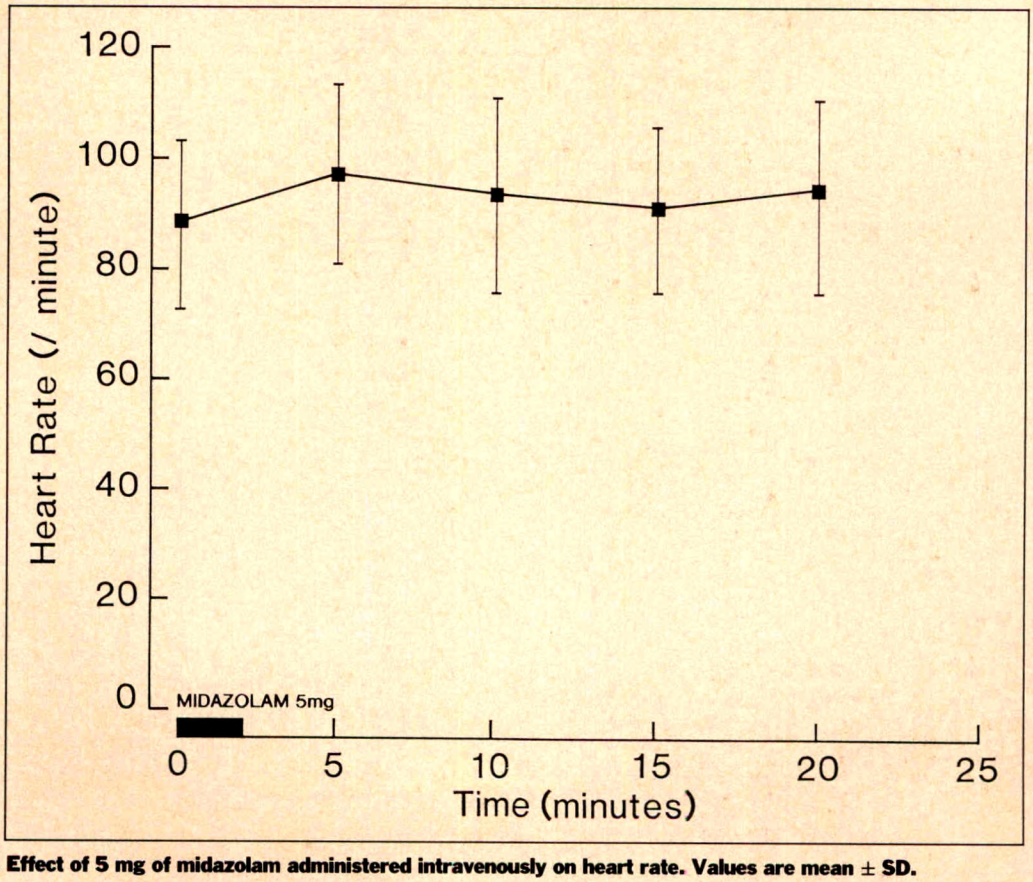


FIGURE 2. Effect of 5 mg of midazolam administered intravenously on heart rate. Values are mean ± SD.

TABLE III Effects of Midazolam on Patients with Atrioventricular Junctional Reentry Tachycardia

	SVT Cycle Length (ms)		AVNFP ERP (ms)		Isoproterenol Needed for SVT Induction	
Pt No.	C	M	C	M	C	M
1	308	306	—	—	+	o
7	292	280	340	320	+	+
13	360	320	360	320	+	+
16	300	288	—	—	+	+
17	260	280	340	320	+	+
19	450	430	400	400	o	o

AVNFP ERP = atrioventricular node fast pathway effective refractory period; other abbreviations as in Table II.

lam on anterograde conduction are similar to those of diazepam. Atrial and ventricular effective refractory periods were unchanged, and AV and VA Wenckebach cycle lengths showed no significant alteration. Sinus node function was unchanged. The moderate hypotensive effect of midazolam usually caused a reflex tachycardia. This increase in sympathetic tone caused a minor decrease in AV node effective refractory period that was statistically insignificant in the relatively small number of cases in which it could be measured in this study. In contrast with diazepam,[15] dual AV junctional pathways were still demonstrable after midazolam was administered in the 4 patients with AV junctional reentry tachycardia. VA conduction showed only minor changes (prolongation) in VA Wenckebach and effective refractory periods.

Effects on tachycardia induction: The lack of significant effect on inducibility of tachycardia by intravenous midazolam is in accordance with the lack of significant electrophysiologic effects and the minor reflex increase in sympathetic tone that is known to facilitate tachycardia induction.

Perceptions and side effects: Midazolam was well-tolerated and had an excellent sedative effect without significant side effects. A previous study[16] reported that most patients undergoing cardioversion using midazolam as an intravenous sedative had no recollection of the procedure afterwards, whereas the incidence of lack of amnesia is up to 37% after diazepam.[17] There were no clinically significant episodes of hypotension or respiratory depression.

In conclusion, midazolam, which has no significant electrophysiologic effect, is an excellent sedative for patients undergoing electrophysiologic studies.

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Use-Dependent Electrophysiologic Effects of Amiodarone in Coronary Artery Disease and Inducible Ventricular Tachycardia

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Amiodarone produces use-dependent block of cardiac sodium channels in vitro. This study assessed whether similar use-dependent block occurred in 19 patients with coronary artery disease and inducible, sustained, monomorphic ventricular tachycardia treated with amiodarone. Beat-to-beat measurements of ventricular paced QRS durations during 12-beat trains at cycle lengths of 700, 600, 400 and 300 ms were analyzed at a baseline antiarrhythmic drug-free study and after 2 and 10 weeks of amiodarone therapy. At the drug-free study, there were no significant changes in paced QRS durations within the 12-beat trains at any pacing cycle lengths. After 2 and 10 weeks of amiodarone therapy, progressive prolongation of paced QRS durations occurred over the 12-beat trains at pacing cycle lengths of 600, 400 and 300 ms ($p < 0.05$). Significant changes in QRS duration were not observed at a pacing cycle length of 700 ms. This progressive prolongation in QRS duration can be fitted as a function of beat number to a monoexponential equation and occurred with an onset time constant of 1.02 ± 0.41 beats (306 ± 122 ms) at a pacing cycle length of 300 ms. The magnitude of QRS prolongation increased as the pacing cycle length was shortened. The magnitudes of QRS prolongation were similar after 2 and 10 weeks of amiodarone therapy. In conclusion, use-dependent prolongation in QRS duration occurs at rapid pacing cycle lengths in humans receiving amiodarone.

(Am J Cardiol 1992;70:598–604)

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Amiodarone is one of the most effective antiarrhythmic agents used clinically.[1–3] It is the only antiarrhythmic agent studied that has been shown to improve mortality in patients with ventricular arrhythmias.[4] It is both a potassium[5–6] and a sodium[7–13] channel blocker. The latter has been experimentally shown to exhibit use-dependence[7–12] reflecting time- and state-dependent interactions of amiodarone with sodium channels.[14–16] Use-dependent sodium channel blockade by antiarrhythmic agents can be estimated by measuring changes in QRS duration after an abrupt change in stimulation frequency.[17–18] This clinical measure of conduction velocity is correlated with intraventricular conduction[18–19] that has been found to be related to the maximal rate of rise of phase 0 of the action potential ($\dot{V}_{max}$).[19–21] The kinetics of onset of use-dependent prolongation in QRS duration by amiodarone were recently reported in a few patients[17]; however, the time course of onset of use-dependent block during chronic amiodarone loading has not been reported. The effects of stimulation rate on the kinetics of onset of use-dependent block have not been studied in humans. This study was designed to determine the rate-dependence of the kinetics and the time course of onset of use-dependent prolongation in QRS duration at 2 and 10 weeks after initiation of amiodarone therapy in patients with ischemic heart disease and inducible ventricular tachycardia (VT).

METHODS

Study patients: Patients presenting with symptomatic VT or ventricular fibrillation were eligible for participation in this study. All patients had inducible, sustained, monomorphic VT during electrophysiologic studies in an antiarrhythmic drug-free condition. Nineteen consecutive consenting patients were enrolled. This study was approved by the conjoint medical ethics committee of the University of Calgary and the Foothills Hospital.

Electrophysiologic studies: Baseline electrophysiologic studies were performed after antiarrhythmic medications were withdrawn for ≥5 half-lives and were repeated 2 and 10 weeks after initiation of amiodarone therapy in a standardized dosage. The initial daily dosage was 1,200 mg for 14 days. The daily dosage was then reduced to 800 mg for the next 7 days. Thereafter, the daily maintenance dosage was 400 mg.

Cardiac pacing was performed using a programmable stimulator (Bloom Associates, Flying Hills, Pennsylvania) with stimuli of twice diastolic threshold intensity

and pulse widths of 2 ms in duration.[22] Surface electrocardiographic leads I, aVF and V_1 were recorded simultaneously with intracardiac electrograms from the high right atrium, His bundle position and right ventricular apex at a paper speed of 200 mm/s (Mingograf, Siemens-Elema, Stockholm, Sweden). The protocol used to assess the use-dependent prolongation in QRS duration consisted of 12-beat pacing trains from the right ventricular apex at cycle lengths of 700, 600, 400 and 300 ms. Ventricular pacing was initiated during sinus rhythm, and the onset of the pacing train was coupled to the last sinus beat at the selected RR interval. Patients were allowed to recover for ≥2 minutes between each pacing train. The 300 ms pacing train was repeated at the conclusion of other pacing protocols used in another study. The purpose was to document reproducibility of the measurement and to demonstrate the absence of cumulative hemodynamic effects resulting from the sequence of stimulation. All pacing protocols were performed before VT induction to avoid sympathetic stimulations that may interfere with the drug effects.

Ventricular effective refractory period was determined using extrastimulus technique after 8-beat trains of 700, 600, 400 and 300 ms. Each pacing train was separated by a 30-second pause. The extrastimulus was decremented by 10 ms until there was loss of capture. Ventricular effective refractory period was defined as the longest coupling interval that resulted in loss of capture. For the VT induction protocol, 1, 2 and 3 extrastimuli were applied to the right ventricular apex after 8-beat trains of 600, 500, and 400 ms. Thereafter, 6- and 12-beat trains of right ventricular decremental pacing were performed beginning at a cycle length of 300 ms and decreasing by 10 ms, until 2:1 block occurred. If VT was not reproducibly induced, the stimulation was repeated from the right ventricular outflow tract. The end point of the study was completion of the protocol or induction of sustained VT. VT was defined as ≥5 consecutive ventricular beats at a cycle length of ≤500 ms and was considered sustained when it persisted for >30 seconds or needed termination because of hemodynamic compromise. Effective antiarrhythmic therapy was that which prevented induction of VT (<5 beats).

Data and statistical analysis: Use-dependent sodium channel blockade by amiodarone was defined as a progressive prolongation in paced QRS durations within the 12-beat train. Beat-to-beat measurements of paced QRS durations were analyzed from surface electrocardiographic leads I, aVF and V_1 at a paper speed of 200 mm/s. The onset and offset of the QRS complex were defined as the earliest and latest rapid deflections, respectively, across the baseline. The measurements were obtained by 2 independent observers. The second observer was unaware of the treatment status of patients, the pacing cycle lengths or the order of QRS complexes. Thus, all QRS complexes were separated, coded and measured, and then the results were reconstructed.

To assess the time course of onset of prolongation of paced QRS duration, the paced QRS duration was normalized relative to that of the first beat (QRS_1/QRS_t) and fitted as a function of beat number to a monoexponential equation using computer software (MINSQ software, MicroMath Inc.): $QRS_1/QRS_t = QRS_1/QRS_{SS} + (1 - QRS_1/QRS_{SS})\exp[(1 - t)/\tau]$, where QRS_1, QRS_t, QRS_{SS} are the QRS durations of the first paced beat, t^{th} beat and at steady state, respectively, and τ is the time constant expressed in terms of beat number. The magnitude of use-dependent QRS prolongation at each pacing cycle length was calculated as $QRS_{SS} - QRS_1$.

Other measurements included: (1) sinus cycle lengths during baseline and after 2 and 10 weeks of amiodarone therapy determined from the mean of 5 successive cycles, and (2) QT interval of the last paced beat of the 12-beat trains at pacing cycle lengths of 700, 600, 400 and 300 ms.

Continuous data are presented as mean ± 1 SD. One-way analysis of variance with repeated measures and 2-way analysis of variance with Duncan's multiple range test were used to examine the differences within groups. The magnitude of use-dependent QRS prolongation after 2 and 10 weeks of amiodarone therapy were compared by a paired *t* test. Multiple linear regression analysis was used to assess the degree of correlation between VT cycle lengths and the following electrophysiologic parameters: (1) ventricular effective refractory period at basic cycle lengths of 700, 600, 400 and 300 ms, (2) paced QT interval of the 12th paced beat at pacing cycle lengths of 700, 600, 400 and 300 ms, and (3) QRS duration of the 12th paced beat at pacing cycle lengths of 700, 600, 400 and 300 ms. These electrophysiologic measurements at baseline and after 2 and 10 weeks of amiodarone therapy were correlated to the corresponding VT cycle lengths for each patient. The correlations were performed separately for measurements obtained from different pacing cycle lengths. The null hypothesis was rejected when the 2-tailed p value was <0.05.

RESULTS

Study patients: The study comprised 17 men and 2 women (mean age 63 ± 9 years). All patients had coro-

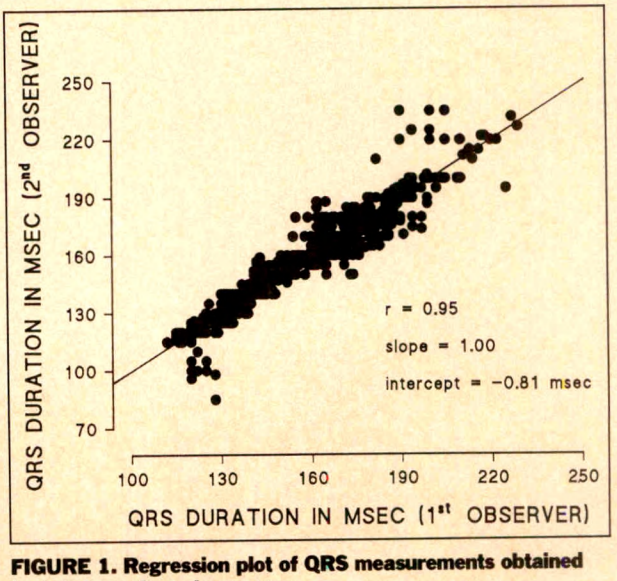


FIGURE 1. Regression plot of QRS measurements obtained by 2 independent observers.

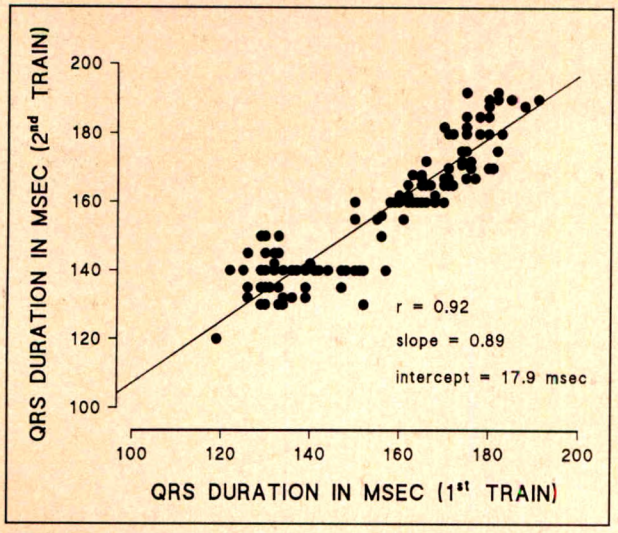


FIGURE 2. Regression plot of QRS measurements of two 300 ms pacing trains that were obtained at beginning and conclusion of pacing protocol.

nary artery disease and remote myocardial infarction with reduced left ventricular ejection fractions (0.36 ± 0.13). Twelve patients presented with symptomatic sustained VT, and 7 had been resuscitated from sudden cardiac death. Sinus cycle lengths were significantly increased at 2 (917 ± 142 ms) and 10 (970 ± 155 ms) weeks compared with at baseline (810 ± 128 ms; p <0.05); however, the difference between 2 and 10 weeks was not statistically significant.

Measurement of paced QRS durations: There was good agreement between the measurements obtained by the 2 observers. Figure 1 shows the linear regression between QRS measurements obtained by the 2 observers. The correlation coefficient was 0.95 ($p < 0.0001$), with a slope of 1 and an intercept of −0.81 ms.

Figure 2 shows the linear regression of QRS durations of the two 300 ms pacing trains that were obtained at the beginning and conclusion of the pacing protocol. The measurements were obtained by the same observer. The correlation coefficient was 0.92 ($p < 0.0001$), with a slope of 0.89 and an intercept of 17.9 ms. This demonstrated a good reproducibility of the measurements, as well as the absence of cumulative hemodynamic effects from the pacing protocol on the QRS measurements.

Use-dependent effects on QRS duration: Figure 3 summarizes the results of the beat-by-beat analysis of paced QRS duration at pacing cycle lengths of 700, 600, 400 and 300 ms before and after 2 weeks of amiodarone therapy. At baseline, there were no significant increases in paced QRS durations within the 12-beat trains at any pacing cycle length. In contrast, after 2 weeks of amiodarone therapy, statistically significant prolongation of the paced QRS durations occurred over the 12-beat trains at pacing cycle lengths of 600, 400 and 300 ms, but not at a cycle length of 700 ms. The result after 10 weeks of amiodarone therapy (not

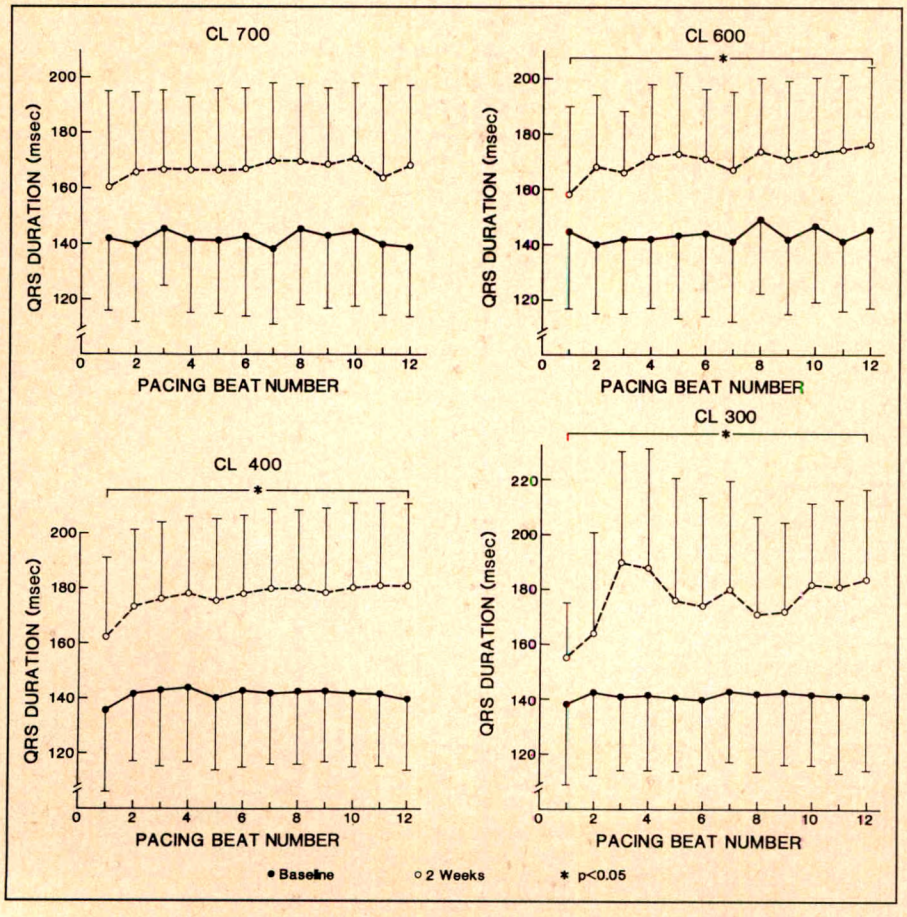


FIGURE 3. Mean ± 1 SD beat-by-beat paced QRS durations at different pacing cycle lengths (CL) during baseline studies and after 2 weeks of amiodarone therapy.

shown) were comparable to those after 2 weeks. Figure 4 shows analog data illustrating changes in QRS duration after the onset of ventricular pacing at a cycle length of 300 ms at baseline and after 2 and 10 weeks of amiodarone therapy.

Figure 5 shows the time courses of onset of QRS prolongation at the 3 pacing cycle lengths in a representative patient after 2 weeks of amiodarone therapy. The normalized paced QRS duration (QRS_1/QRS_t) was fitted as a function of beat number to a monoexponential

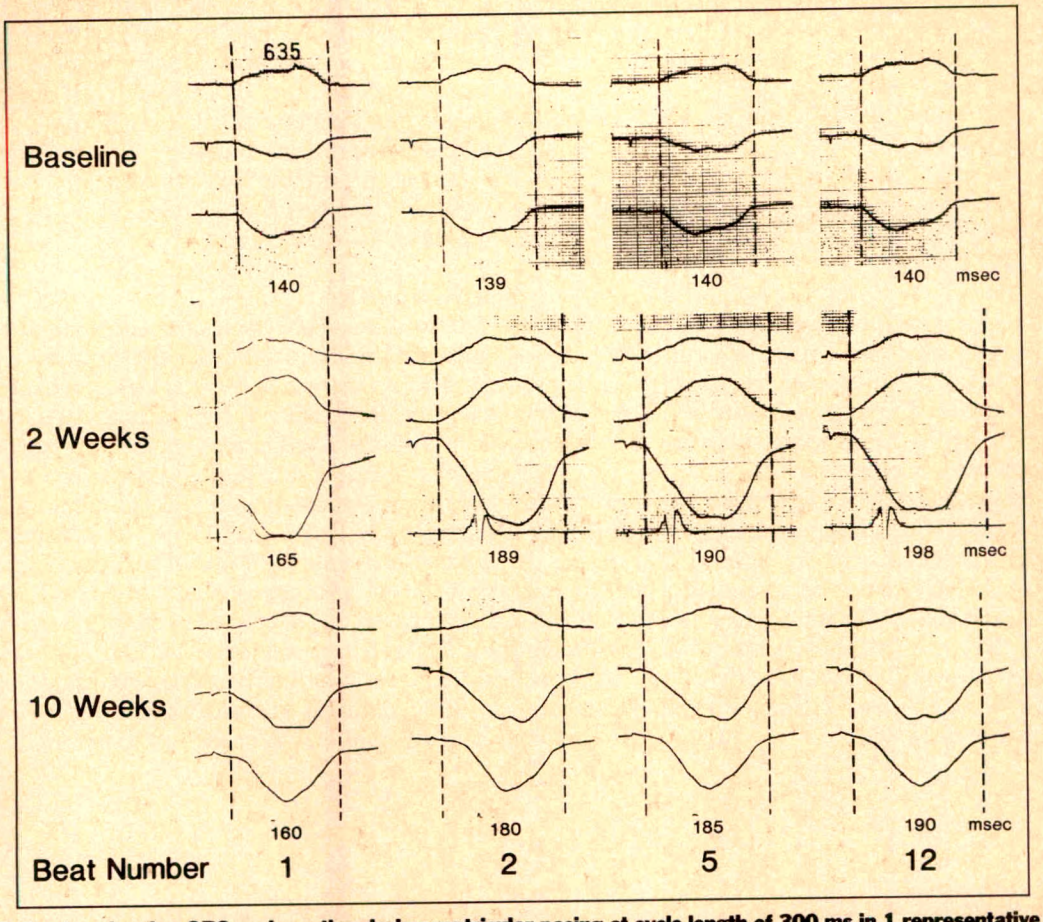


FIGURE 4. Tracing showing QRS prolongation during ventricular pacing at cycle length of 300 ms in 1 representative patient at baseline antiarrhythmic drug-free study and after 2 and 10 weeks of amiodarone therapy. The 1st, 2nd, 5th and 12th beats of the 12-beat pacing trains are shown. *Vertical dotted lines* indicate onset and offset of QRS complex. Measured QRS duration is shown at *bottom* of each complex.

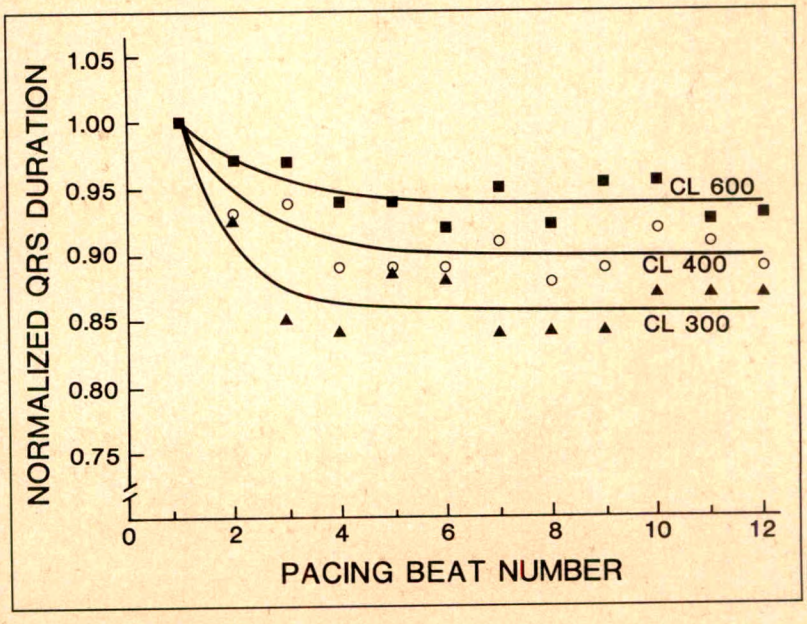


FIGURE 5. Use-dependent effects on QRS duration at different pacing cycle lengths (CL) in 1 representative patient after 2 weeks of amiodarone therapy. Paced QRS duration for each beat in the train was normalized relative to that of first beat and fitted to a monoexponential function (see text).

TABLE I Time Constant of Onset of Amiodarone-Induced Prolongation in QRS Duration Using a Monoexponential Function at Different Pacing Cycle Lengths

	Pacing Cycle Length (ms)		
	600	400	300
	*		
	*		*
τ (ms)	834 ± 752	539 ± 421	306 ± 122
R value	0.83 ± 0.11	0.86 ± 0.11	0.84 ± 0.12

*p <0.05.
R value = correlation coefficient of monoexponential fit; τ = time constant of onset of QRS prolongation.

curve. The means of the correlation coefficients of this analysis and the time constants of onset of QRS prolongation (expressed in ms) at each pacing cycle length are shown in Table I. The time constants of onset of QRS prolongation significantly decreased when the pacing cycle length was shortened ($p < 0.05$).

The magnitude of use-dependent prolongation in QRS duration at each pacing cycle length was calculated as the difference between the paced QRS duration at steady state obtained from the monoexponential fit and that of the first beat in the train. The magnitude of use-dependent QRS prolongation increased as the pacing length was shortened ($p < 0.05$) (Figure 6); this use-dependent effect achieved a maximum within 2 weeks of amiodarone therapy.

Relation between use-dependent prolongation in QRS duration and ventricular tachycardia cycle length: Only a small number of patients were noninducible after 2 and 10 weeks of amiodarone therapy (2 and 1 patient at 2 and 10 weeks, respectively). However, VT cycle lengths were significantly prolonged at 2 and 10 weeks compared with at baseline (Figure 7). Only VTs with same electrocardiographic morphology at each study were used for comparison. With use of multiple linear regression analysis, VT cycle length was linearly and independently correlated to the ventricular effective refractory period, but was not correlated to the QT interval or QRS duration of the 12th paced beat at any pacing cycle length (Table II).

DISCUSSION

Use-dependent effects of amiodarone on QRS duration: This study investigated the electrophysiologic effects of amiodarone in patients with coronary artery disease and inducible VT. We demonstrated a prolongation of QRS duration after abrupt changes to shorter pacing cycle lengths during amiodarone therapy. No significant prolongation of QRS duration was seen at a pacing cycle length of 700 ms. The kinetics of QRS prolongations during rapid pacing trains can be described by a monoexponential process, with shorter time constants as the pacing cycle lengths were decreased. Furthermore, the magnitude of QRS prolongation was greater at shorter pacing cycle lengths.

QRS duration was used in this study as an in vivo index of drug-induced conduction slowing. The results

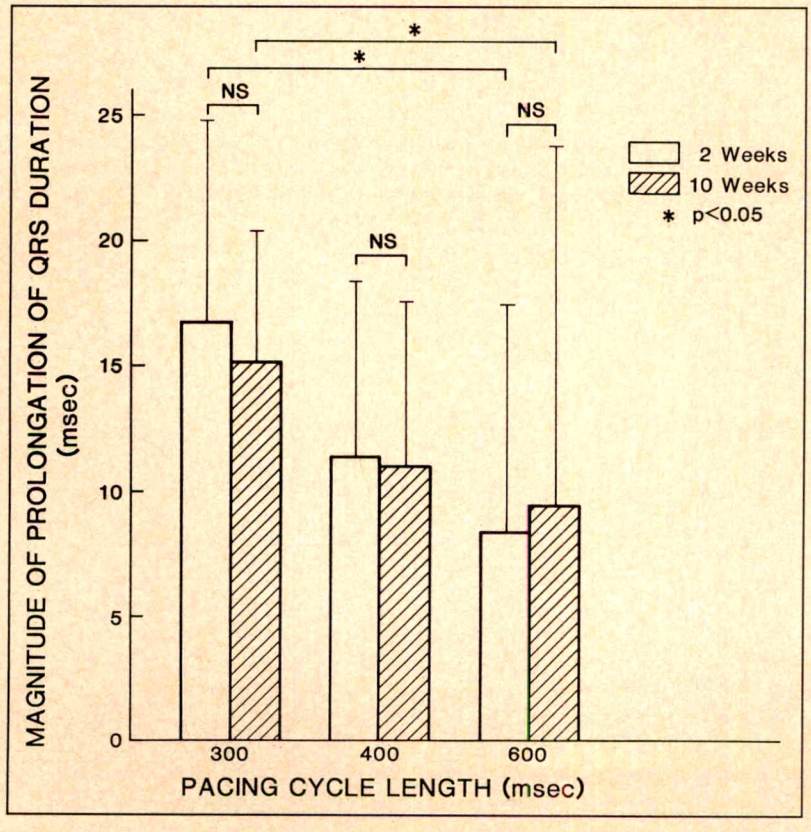


FIGURE 6. Magnitude and time course of onset of use-dependent QRS prolongation during amiodarone loading. Magnitude of QRS prolongation compared among different pacing cycle lengths and between 2 and 10 weeks of amiodarone therapy. NS = not significant.

TABLE II Correlations of Ventricular Tachycardia Cycle Lengths and Different Electrophysiologic Parameters at Baseline and 2 and 10 Weeks After Amiodarone Therapy as Assessed by Multivariate Analysis

Electrophysiologic Parameters	Baseline	2 Weeks	10 Weeks	R Value	p Value
CL 700 ms					
VERP	266 ± 28	319 ± 36	311 ± 29	0.52	0.006
QT	443 ± 41	488 ± 68	471 ± 26	0.16	0.42
QRS	139 ± 25	169 ± 29	167 ± 22	0.25	0.32
CL 600 ms					
VERP	259 ± 21	299 ± 27	297 ± 34	0.51	0.002
QT	430 ± 41	465 ± 50	455 ± 35	−0.05	0.78
QRS	144 ± 27	175 ± 28	172 ± 23	0.25	0.15
CL 400 ms					
VERP	237 ± 18	271 ± 22	271 ± 25	0.37	0.04
QT	390 ± 28	437 ± 36	434 ± 38	0.22	0.25
QRS	140 ± 26	182 ± 31	179 ± 27	−0.11	0.58
CL 300 ms					
VERP	219 ± 16	231 ± 17	239 ± 21	0.43	0.03
QT	374 ± 27	408 ± 20	396 ± 33	0.42	0.09
QRS	141 ± 26	185 ± 33	190 ± 24	−0.32	0.22

Values are mean ± SD (ms).
CL = pacing cycle length; QRS = QRS duration of last paced beat of 12-beat train; QT = QT interval of last paced beat of 12-beat train; VERP = ventricular effective refractory period.

demonstrated a rapid onset of QRS prolongation, with an onset time constant of 1.02 ± 0.41 beats (306 ± 122 ms) at a pacing cycle length of 300 ms. This is in accordance with previous experimental data. Anderson et al[11] investigated the use-dependent depression of conduction velocity by amiodarone in canine ventricular myocardium in vivo and found that 67% of the change occurred between the first 2 beats of the rapid train, with little change occurring after the 10th beat.[11] Varro et al[12] found use-dependent block of $\dot{V}_{max}$ in guinea pig papillary muscle to achieve a maximum after 4.2 ± 0.7 pulses at a pacing cycle length of 300 ms. A recent study of a smaller number of patients showed results comparable to ours. The onset time constant was 3.6 ± 2.0 beats in 6 patients treated with amiodarone.[17]

Our results further show that the onset time constants and the magnitude of QRS prolongation are dependent on the pacing cycle lengths. This is in agreement with previous in vitro data.[8,23] Furthermore, similar to results on $\dot{V}_{max}$ depression from Mason et al, QRS duration of the third and fourth beats at pacing cycle lengths of 300 ms was more prolonged than that of subsequent beats.[8] This may be explained by the increase in repolarization induced by amiodarone such that the first few beats occurred before completion of the repolarization process. Rate-related reduction in action potential duration eliminated this effect during subsequent beats.

Relation between use-dependent prolongation in QRS duration and ventricular tachycardia cycle length: In the present study, VT cycle length was significantly correlated to ventricular effective refractory period, but not to ventricular conduction. Magnitude of QRS duration of the 12th paced beat at different pacing cycle lengths was used to assess the effect of amiodarone on ventricular conduction. However, one cannot imply a definite causal relation. Ventricular effective refractory period was measured in the right ventricle, and conduction was estimated from surface QRS duration. Therefore, these measured electrophysiologic effects of refractoriness and conduction may not reflect similar changes occurring within the reentrant circuit of the VT. Furthermore, one previous study showed that procainamide resulted in prolongation of VT cycle length, which correlated with drug-induced QRS prolongation.[24] Our study of the correlation observed for amiodarone with prolongation of ventricular effective refractory period was similar to that for propafenone.[25] This suggests that amiodarone may affect VT by a mechanism that is similar to propafenone, but different from procainamide. This correlation of prolongation of VT cycle length with ventricular refractory period rather than QRS duration has been explained on the basis that the drug effect on

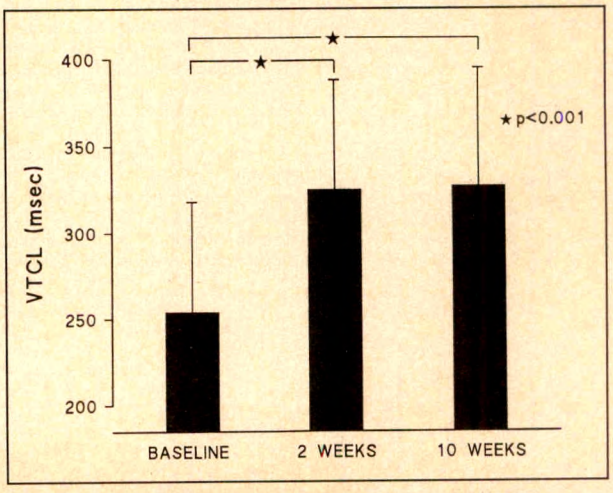


FIGURE 7. Ventricular tachycardia cycle length (VTCL) at baseline antiarrhythmic drug-free study and after 2 and 10 weeks of amiodarone therapy. Values are mean ± 1 SD. *p <0.05 compared with baseline.

conduction may occur through partially refractory tissue as opposed to fully repolarized tissue in the circuit.[25] However, further studies in in vivo and in vitro experimental models of reentrant arrhythmias are needed to clarify this issue.

Study limitations: Surface QRS duration was used as an estimate of conduction velocity in this study. Intraventricular conduction time is determined by a number of active and passive membrane properties, only one of which is $\dot{V}_{max}$.[26–28] Furthermore, $\dot{V}_{max}$ may not reflect the inward sodium current in a strictly linear manner.[29–30] Thus, the clinical measures used in the present investigation are approximate and indirect. However, a recent study of humans provides evidence for the use of QRS duration as a measure of sodium channel blockade by several antiarrhythmic agents, including amiodarone.[17] A good correlation between our study and previous experimental data further supports the validity of the aforementioned assumption.

Twelve-beat ventricular pacing trains at different cycle lengths were used in our study to assess the effects of amiodarone on QRS prolongation. Although one study found that the use-dependent block of $\dot{V}_{max}$ induced by amiodarone did not reach steady state by the end of the 19-beat train,[8] a number of others agreed that most of the drug effect occurred within the first few beats of rapid pacing trains and that little change occurred after the tenth beat.[9,11–12]

Acknowledgment: We would like to acknowledge the technical assistance of Peggy R. Cassidy, and the secretarial assistance of Bev Shea and Heather Price in the preparation of this manuscript.

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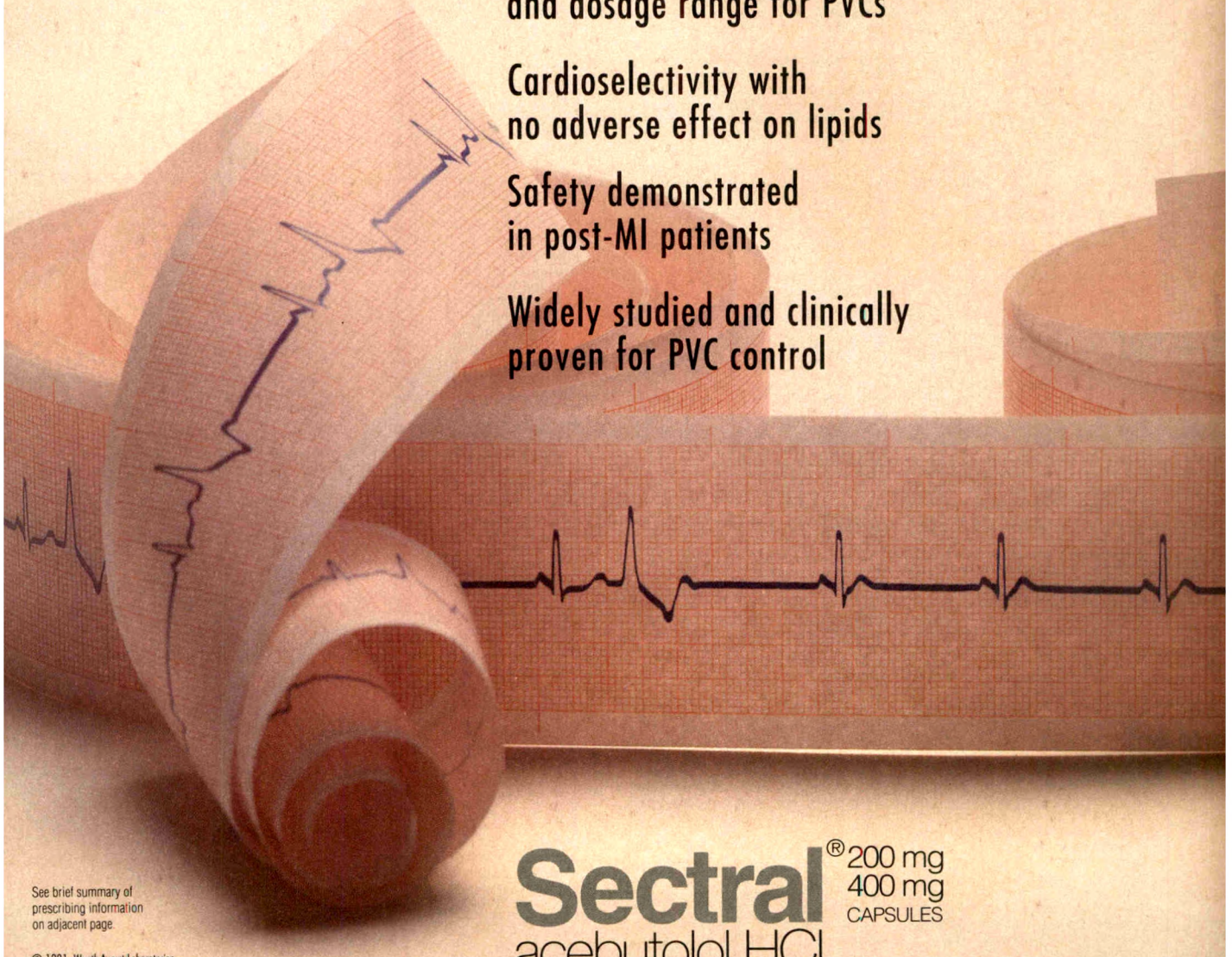
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An established starting dose and dosage range for PVCs

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Widely studied and clinically proven for PVC control



Sectral® 200 mg 400 mg CAPSULES
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THE CARDIOSELECTIVE BETA BLOCKER FOR PVC CONTROL

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THE CARDIOSELECTIVE BETA BLOCKER FOR PVC CONTROL

Usual starting dose	**200 mg b.i.d.**
Optimal PVC response	**600 mg to 1200 mg per day**
Use in elderly	**Doses above 800 mg per day should be avoided**

(Brief Summary. See Package Circular for full prescribing information.)

CONTRAINDICATIONS: SECTRAL is contraindicated in: 1) persistently severe bradycardia; 2) second- and third-degree heart block; 3) overt cardiac failure; 4) cardiogenic shock. (See WARNINGS)

WARNINGS: Cardiac Failure: Sympathetic stimulation may be essential for support of circulation in patients with diminished myocardial contractility and inhibition by β-adrenergic receptor blockade may precipitate more severe failure. Although β-blockers should be avoided in overt cardiac failure, SECTRAL can be used cautiously when heart failure is controlled with digitalis and/or diuretics. Digitalis and SECTRAL impair AV conduction. Withdraw SECTRAL if cardiac failure persists.

In Patients Without a History of Cardiac Failure: In patients with aortic or mitral valve disease or compromised left ventricular function, continued depression of the myocardium with β-blockers over time may lead to cardiac failure. Digitalize patients at first signs of failure, and/or give a diuretic and observe closely. Withdraw SECTRAL if cardiac failure persists.

Exacerbation of Ischemic Heart Disease Following Abrupt Withdrawal: Abrupt discontinuation of some β-blockers in coronary artery disease patients may exacerbate angina; in some cases, myocardial infarction and death have been reported. Caution such patients against interruption of therapy without a physician's advice. Even in the absence of overt ischemic heart disease, withdraw SECTRAL gradually over a period of about two weeks; observe carefully and advise patients to minimize physical activity during this time. (If desired, patients may be transferred directly to comparable doses of an alternative β-blocker without interruption of β-blocking therapy.) If exacerbation of angina occurs, restart full-dose anti-anginal therapy immediately and hospitalize patient until stabilized.

Peripheral Vascular Disease: β-antagonists reduce cardiac output and can precipitate/aggravate arterial insufficiency in patients with peripheral or mesenteric vascular disease. Exercise caution and observe such patients closely for progression of arterial obstruction.

Bronchospastic Diseases: Patients with Bronchospastic Disease Should, in General, Not Receive a β-Blocker. Because of its relative β_1-selectivity, low doses of SECTRAL may be used cautiously in such patients who do not respond to, or cannot tolerate, alternative treatment. Since β_1-selectivity is not absolute and is dose-dependent, use lowest possible dose of SECTRAL initially, preferably in divided doses. Make bronchodilator, e.g., theophylline, or a β_2-stimulant, available in advance with instructions for use.

Anesthesia and Major Surgery: The necessity/desirability of withdrawing β-blockers prior to major surgery is controversial; the heart's impaired ability to respond to β-adrenergically mediated reflex stimuli may enhance the risk of excessive myocardial depression during general anesthesia. Difficulty in restarting and maintaining the heartbeat also has been reported with beta-blockers. If treatment is continued, take special care when using anesthetics that depress the myocardium; use lowest possible SECTRAL dose. SECTRAL, like other β-blockers, is a competitive inhibitor of β-receptor agonists, so its effects can be reversed by cautious administration of such agents (e.g., dobutamine or isoproterenol). Symptoms of excessive vagal tone (e.g., profound bradycardia, hypotension) may be corrected with atropine.

Diabetes and Hypoglycemia: β-blockers may potentiate insulin-induced hypoglycemia and mask some symptoms such as tachycardia; dizziness and sweating are usually not significantly affected. Warn diabetics of possible masked hypoglycemia.

Thyrotoxicosis: β-adrenergic blockade may mask some clinical signs (tachycardia) of hyperthyroidism. Abrupt withdrawal of SECTRAL may precipitate a thyroid storm in patients suspected of developing thyrotoxicosis.

PRECAUTIONS: Impaired Renal or Hepatic Function: While there are no U.S. studies, foreign published experience shows that acebutolol has been used successfully in chronic renal insufficiency. Acebutolol is excreted via the G.I. tract, but the active metabolite, diacetolol, is eliminated mainly by the kidney. A linear relationship exists between renal clearance of diacetolol and creatinine clearance (Cl_{cr}); reduce daily dose of acebutolol by 50% when Cl_{cr} is less than 50 mL/min and by 75% when it is less than 25 mL/min. Use cautiously in patients with impaired hepatic function.

SECTRAL has been used successfully and without problems in elderly patients in U.S. clinical trials without specific dosage adjustment. However, in the elderly, lower maintenance doses may be required because bioavailability of SECTRAL and its metabolite are approximately doubled.

Information for Patients: Warn patients, especially those with evidence of coronary artery disease, against interruption or discontinuation of SECTRAL without physician supervision. Although cardiac failure rarely occurs in properly selected patients, advise patients to consult a physician if signs or symptoms suggestive of impending CHF, or unexplained respiratory symptoms, develop.

Warn patients of possible severe hypertensive reactions from concomitant use of α-adrenergic stimulants, e.g., nasal decongestants used in OTC cold medicines and nasal drops.

Clinical Laboratory Findings: SECTRAL, like other β-blockers has been associated with development of antinuclear antibodies (ANA). In prospective clinical trials, patients receiving SECTRAL had a dose-dependent increase in the development of positive ANA titers. Symptoms related to this laboratory abnormality were infrequent. Symptoms and ANA titers were reversible upon discontinuation of SECTRAL.

Drug Interactions: Catecholamine-depleting drugs may have additive effects when given with β-blockers. Observe patients treated with both agents closely for evidence of marked bradycardia or hypotension which may present as vertigo, syncope/presyncope, or orthostatic changes in blood pressure without compensatory tachycardia. Exaggerated hypertensive responses have been reported from use of β-adrenergic antagonists with α-adrenergic stimulants, including those in OTC cold remedies and vasoconstrictive nasal drops. Nonsteroidal anti-inflammatory drugs may blunt antihypertensive effects of beta-blockers.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Chronic oral toxicity studies in rats and mice, at doses 15 times the maximum recommended (60 kg) human dose, did not indicate carcinogenic potential for SECTRAL. Diacetolol, the major metabolite in man, was without carcinogenic potential in rats at doses up to 1800 mg/kg/d. SECTRAL and diacetolol also had no mutagenic potential in the Ames Test. No significant impact on reproductive performance or fertility was found in rats following SECTRAL or diacetolol doses of up to 240 or 1000 mg/kg/d, respectively.

Pregnancy: *Teratogenic Effects:* Pregnancy Category B: No teratogenic effects were seen in rat or rabbit reproduction studies utilizing SECTRAL doses that were, respectively, approximately 31.5 and 6.8 times the maximum recommended human dose. At this dose in the rabbit, slight fetal growth retardation was noted; this was considered to be a result of maternal toxicity (evidenced by reduced food intake, lowered rate of body weight gain, mortality). Diacetolol studies (doses up to 450 mg/kg/d in rabbits and up to 1800 mg/kg/d in rats) showed no evidence of fetal harm other than a significant elevation in postimplantation loss with 450 mg/kg/d, a level at which food consumption and body weight gain were reduced in rabbit dams; there was a nonstatistically significant increase in incidence of bilateral cataract in rat fetuses from dams treated with 1800 mg/kg/d. There are no adequate and well-controlled trials in pregnant women; SECTRAL should be used during pregnancy only if potential benefit justifies risk to the fetus.

Nonteratogenic Effects: Human studies indicate that acebutolol and diacetolol cross the placenta. Neonates of mothers who received acebutolol during pregnancy have reduced birth weight, decreased blood pressure, and decreased heart rate.

Labor and Delivery: Effect on labor and delivery in pregnant women is unknown. Animal studies have shown no effect of SECTRAL on the usual course of labor and delivery.

Nursing Mothers: Acebutolol and diacetolol appear in breast milk (milk: plasma ratio of 7.1 and 12.2, respectively). Use in nursing mothers is not recommended.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: SECTRAL is well tolerated in properly selected patients. Most adverse effects have been mild, not required therapy discontinuation, and tended to decrease as treatment duration increases.

The incidence of treatment-related side effects (volunteered and elicited) derived from U.S. controlled clinical trials in patients with hypertension, angina and arrhythmia follows. Numbers represent percentage incidence for SECTRAL (N =1002) versus placebo (N=314), respectively.

Cardiovascular: Chest pain 2%, 1%; Edema 2%, 1%. *CNS:* Depression 2%,1%; Dizziness 6%, 2%; Fatigue 11%, 4%; Headache 6%, 4%; Insomnia 3%, 1%; Abnormal dreams 2%, 1%. *Dermatologic:* Rash 2%, 1%. *Gastrointestinal:* Constipation 4%, 0%; Diarrhea 4%, 1%; Dyspepsia 4%, 1%; Flatulence 3%, 1%; Nausea 4%, 0%. *Genitourinary:* Micturition (frequency) 3%, <1%. *Musculoskeletal:* Arthralgia 2%, 2%; Myalgia 2%, 0%. *Respiratory:* Cough 1%, 0%; Dyspnea 4%, 2%; Rhinitis 2%, <1%. *Special Senses:* Abnormal Vision 2%, 0%.

The following selected (potentially important) side effects were seen in up to 2% of SECTRAL patients: *Cardiovascular:* hypotension, bradycardia, heart failure. *CNS:* anxiety hyper/hypoesthesia, impotence. *Skin:* pruritus. *Gastrointestinal:* vomitting, abdominal pain. *Genitourinary:* dysuria, nocturia. *Liver and Biliary:* small number of reported cases of liver abnormalities (increased SGOT, SGPT, LDH). In some cases, increased bilirubin or alkaline phosphatase, fever, malaise, dark urine, anorexia, nausea, headache, and/or other symptoms have been reported. In some cases, symptoms and signs were confirmed by rechallenge. Abnormalities were reversible upon drug cessation. *Musculoskeletal:* back and joint pain. *Respiratory:* pharyngitis, wheezing. *Special Senses:* conjunctivitis, dry eye, eye pain. *Autoimmune:* extremely rare reports of systemic lupus erythematosis.

Incidence of drug-related adverse effects (volunteered and solicited) based on SECTRAL dose is shown below. (Data from 266 hypertensive patients treated for 3 months on a constant dose.)

Body System	400 mg/day (N = 132)	800 mg/day (N = 63)	1200 mg/day (N = 71)
Cardiovascular	5%	2%	1%
Gastrointestinal	3%	3%	7%
Musculoskeletal	2%	3%	4%
Central Nervous System	9%	13%	17%
Respiratory	1%	5%	6%
Skin	1%	2%	1%
Special Senses	2%	2%	6%
Genitourinary	2%	3%	1%

Potential Adverse Effects: Certain adverse effects not listed above have been reported with other β-blocking agents and should be considered as potential adverse effects of SECTRAL.

CNS: Reversible mental depression progressing to catatonia, an acute syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.

Cardiovascular: Intensification of AV block (see CONTRAINDICATIONS). *Allergic:* Erythematous rash, fever with aching and sore throat, laryngospasm, respiratory distress.

Hematologic: Agranulocytosis, nonthrombocytopenic and thrombocytopenic purpura.

Gastrointestinal: Mesenteric arterial thrombosis, ischemic colitis.

Miscellaneous: Reversible alopecia, Peyronie's disease. The oculomucocutaneous syndrome associated with practolol has not been reported with SECTRAL.

Keep at room temperature, Approximately 25°C (77°F).

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Reproducibility of a Symptomatic Response to Upright Tilt in Young Patients with Unexplained Syncope

Frank A. Fish, MD, Janette F. Strasburger, MD, and D. Woodrow Benson, Jr., MD, PhD

Serial upright tilt testing has been advocated as a possible therapeutic end point in treating patients with recurrent syncope, but the reproducibility of such testing has not been well-established in the absence of therapy. In 21 patients with recurrent syncope and a symptomatic response to upright tilt testing, tilt was repeated following a 25- to 30-minute recovery. Syncope or presyncope was reproduced in 14 of 21 patients on repeat tilt; 4 of 21 patients experienced milder symptoms, and 3 of 21 patients remained entirely asymptomatic on repeat tilt. The pattern of physiologic response was different during initial and repeat tilt in 7 of the 21 patients. Blood pressure and heart rate (before and during symptoms) were similar for the group on initial and repeat tilt. The abnormal physiologic response and associated symptoms elicited during upright tilt testing for unexplained syncope can be reproduced on immediate repeat tilt testing in most patients. However, the frequently attenuated response during repeat testing may limit its use as a therapeutic end point in individual patients.

(Am J Cardiol 1992;70:605–609)

Serial upright tilt testing has been advocated as a means of assessing therapeutic efficacy in patients with recurrent syncope and a positive tilt test.[1–3] However, the reproducibility of the response to upright tilt in the absence of treatment has not been well-defined. We prospectively assessed whether an abnormal response to upright tilt could be reliably reproduced after a brief recovery period in a group of ostensibly healthy young patients undergoing evaluation of recurrent, unexplained syncope with a previously described protocol.[4] Reproducibility was assessed in terms of variables which might serve as possible indicators of a beneficial effect of treatment.

METHODS

Study group: Twenty-one patients (6 male and 15 female patients aged 8 to 19 years (median 14.2) with recurrent, unexplained syncope who developed syncope or presyncope in association with a decline in heart rate or blood pressure were subjected to repeat tilt. During the same period, 7 other patients who remained asymptomatic during initial tilt testing were not subjected to repeat tilt. All patients had undergone a thorough history and physical examination that failed to suggest underlying cardiac or neurologic disorders. In each patient, 12-lead electrocardiogram, 24-hour Holter monitoring and echocardiogram were normal; no patient experienced a syncopal episode during the Holter monitoring. No other diagnostic studies were routinely obtained, although many patients had undergone 1 or more neurologic studies before referral.

Tilt protocol: The upright tilt test protocol has been previously described.[4] Studies were performed as an outpatient procedure after a 1- to 2-hour fast in a quiet, slightly darkened room. All patients or guardians of patients younger than 18 years gave informed consent before the procedure. An intravenous catheter was placed for drug administration. Patients were monitored for 5 to 10 minutes while lying supine on a hydraulic tilt table (Quinton) fitted with a safety restraint, a foot support, and modified to allow rapid descent to the horizontal position. After upright (90°) tilt, patients remained standing for up to 15 minutes in the absence of symptoms. Heart rate and electrocardiogram leads I, II and III were monitored continuously, and 20- to 30-second strips were recorded during each minute of the study. Blood pressure was monitored by Dinamapp cuff at 1-minute intervals throughout the study. With the emergence of any symptoms or alterations in heart rate and blood pressure, the electrocardiogram was recorded continuously and blood pressure was recorded at the maxi-

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mal frequency (every 30 seconds). If syncope or presyncope developed, the table was quickly returned to the supine position and continuous monitoring was continued until symptoms and cardiovascular changes had resolved. For both the initial and repeat tilt, presyncope (rather than syncope) prompted termination of the tilt and return to the supine position only when accompanied by changes in heart rate or blood pressure response as described below.

If syncope or presyncope did not develop after 15 minutes in the upright position, the patient was returned to the supine position, and low-dose infusion of isoproterenol was administered (0.02 to 0.04 μg/kg/min). Supine monitoring was continued until stable heart rate and blood pressure were recorded over ≥4 consecutive minutes. Tilt was then repeated for 15 minutes or until syncope or presyncope were observed. If syncope or presyncope did not occur after 15 minutes in the upright position during low-dose isoproterenol, the protocol was sequentially repeated (5 minutes supine, 15 minutes upright) at medium-dose (0.04 to 0.059 μg/kg/min) or high-dose (0.06 to 0.072 μg/kg/min) isoproterenol for 15 minutes or until syncope or presyncope occurred.

After recovery from syncope or presyncope in the supine position, patients remained supine for a total recovery period of up to 30 minutes. Subsequently, recording was resumed under the same conditions first resulting in syncope (baseline or low-dose, medium-dose or high-dose isoproterenol infusion), and tilt was repeated. If patients reported mild symptoms during either the initial or repeat tilt without associated decrease in heart rate or blood pressure, they were asked to remain upright for up to 15 minutes or until symptoms either resolved or progressed to syncope or presyncope. Likewise, if transient changes in heart rate or blood pressure were observed without associated syncope or presyncope, patients remained standing for up to 15 minutes or until symptoms developed. After the repeat tilt, the patient was returned to the supine condition and was monitored until sufficiently recovered to ambulate normally. If syncope or presyncope were not produced under the conditions of the initial symptomatic tilt, the study was terminated.

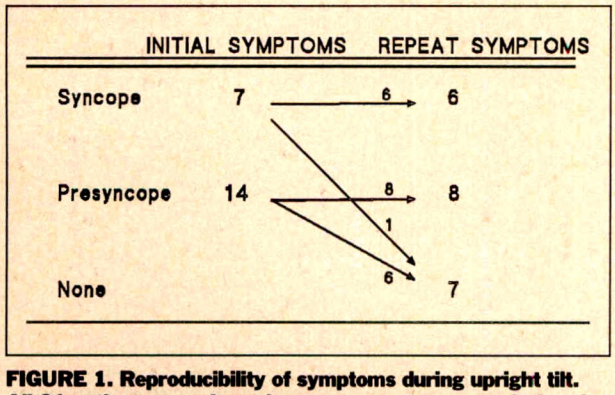


FIGURE 1. Reproducibility of symptoms during upright tilt. All 21 patients experienced syncope or presyncope during the initial tilt *(left column)*. Identical symptoms were elicited in 14 of the patients during repeat tilt, but no symptoms of presyncope or presyncope were elicited in the remaining 7 patients. Of these 7 patients, 4 had transient but discernible physiologic abnormalities that resolved while remaining standing and did not progress to syncope or presyncope.

Definitions and data analysis: Syncope was defined as an abrupt, transient loss of consciousness associated with loss of muscle tone. Presyncope was defined as a sensation of impending loss of consciousness, characterized by lightheadedness, weakness, blurred or altered vision, auditory loss or incoherence. Time to symptom development during the initial tilt was characterized as the time from reaching the upright position to the development of syncope or presyncope requiring lowering of the tilt table. During the repeat tilt, time to symptom development was defined as time to presyncope or syncope or as the time when a maximal discernible decrease in heart rate and blood pressure were recorded (if no symptoms were elicited).

Systolic blood pressure and heart rate during symptoms were compared with averaged values for the 3 minutes before symptom onset (or before the minimal systolic blood pressure or heart rate in the absence of symptoms). Minimal heart rate was determined by averaging the 8 longest consecutive RR intervals from the electrocardiographic recording. Minimal systolic blood pressure was defined as the lowest systolic recording with a correlated heart rate reading from the Dinamapp; if no blood pressure could be obtained during maximal symptoms, systolic blood pressure was defined as 30 mm Hg for statistical calculations.

The patterns of response were defined similar to previously reported observations.[4] A vasodepressor response was defined as a decrease in systolic blood pressure to <80 mm Hg without a heart rate decrease during symptoms. A cardioinhibitory response was defined as an abrupt decrease in heart rate by ≥20% without any antecedent decrease in systolic blood pressure. A mixed response was defined as concurrent decrease in systolic blood pressure <80 mm Hg and a decrease in heart rate by ≥20% compared with averages 3 minutes before onset of symptoms.

Agreement of time to symptom development, minimal systolic pressure, and minimal heart rate of initial and repeat tilt was determined by comparing the fitted regression for each variable (initial versus repeat) to the line of unity. By design, the initial physiologic responses always occurred concurrent with syncope or presyncope. During repeat tilt, the physiologic response was not necessarily linked with concurrent symptoms. An abnormal repeat tilt was defined as any observed decrease in systolic blood pressure <80 mm Hg or decrease in heart rate by ≥20% regardless of associated symptoms. Initial symptoms and initial pattern of physiologic response were compared qualitatively to the results of repeat tilt. Baseline supine heart rate and systolic blood pressure, and 3-minute averages before symptoms were compared (initial versus repeat tilt) for each patient measured with Student's paired *t* test.

RESULTS

Response to initial tilt: All 21 patients had an abnormal physiologic response with associated syncope or presyncope during initial tilt (Figures 1 and 2). Symp-

toms were elicited in the baseline state in 4 patients (syncope in 3, presyncope in 1), during low-dose isoproterenol in 7 patients (syncope in 1, presyncope in 6), medium-dose isoproterenol in 3 patients (syncope in 1, presyncope in 2) and high-dose isoproterenol in 7 patients (syncope in 2, presyncope in 5). The remaining responses were elicited during isoproterenol infusion.

Reproducibility of symptoms (Figure 1): The initial symptomatic response was reproduced on repeat tilt in 14 of 21 patients (Figure 1). There was no difference in reproducibility for symptoms of syncope versus presyncope, although the small numbers might obscure a potentially significant difference ($p > 0.05$, Fisher's exact test). No patient experiencing presyncope during initial tilt experienced syncope on repeat tilt. In contrast, 7 patients remained sufficiently asymptomatic during repeat tilt (despite transient decreases in heart rate or blood pressure in all but 1 patient) that their response to tilt would have been regarded as a "negative" or "inconclusive" by the criteria outlined.

Reproducibility of physiologic pattern of response (Figure 2): On repeat tilt, 18 of 21 patients had an abnormal physiologic response to upright tilt as previously defined. Two others experienced transient but less pronounced slowing of heart rate or blood pressure. However, 8 of these patients experienced a pattern of response on repeat tilt different from their initial pattern of response (Figure 2). No individual pattern of response seemed exclusive of another pattern of response on repeat tilt.

Reproducibility of heart rate and blood pressure changes (Table I and Figures 3, A to C): Individual physiologic variables are summarized in Table I. Systolic blood pressure and heart rate before symptoms (or before maximal physiologic change in patients asymptomatic on repeat tilt) were similar for initial and repeat tilt. This would suggest that the recovery period was "adequate" and that patients experienced similar gravitational and adrenergic stress during both tilts. No statistically significant differences were evident as a group in any aspect of the physiologic response to initial and repeat tilt, though an apparent trend toward attenuated response was suggested ($p > 0.05$, paired t test).

Reproducibility of each variable was also examined by comparing each subjects' values on initial and repeat tilt to the line of identity as displayed in Figures 3, A to C. There was wide variability as would be expected for the various physiologic patterns manifest. The correlation coefficient for heart rate during symptoms improved to $r = 0.89$ when only patients who experienced a decrease in heart rate during both tilts were considered separately (i.e., those with vasodepressor or normal responses during either tilt). The tendency for attenuation in heart rate response during repeat tilt was reflected in 14 of 21 patients (points lying above the line of identity, Figure 3A). Only 3 patients had a greater decrease in heart rate during the repeat tilt.

The correlation of minimal systolic blood pressure during initial and repeat tilt was $r = 0.76$ for all patients (Figure 3B), and $r = 0.75$ for only those with a decrease in blood pressure during both tilts. Again, a weak trend toward attenuation in blood pressure response during the second tilt is suggested in Figure 3C by comparing individual points to the line of identity, and a y-intercept of 10.2 mm Hg (all patients) despite a slope parallel to the line of identity (1.0).

TABLE I Comparison of Physiologic Response to Initial and Repeat Tilt

	Initial Tilt	Repeat Tilt
Systolic BP before symptoms*	107 ± 8 mm Hg	107 ± 15 mm Hg
Minimal systolic BP	63 ± 19 mm Hg	75 ± 25 mm Hg
Mean HR before symptoms*	126 ± 22 beats/min	131 ± 16 beats/min
Minimal HR	88 ± 35 beats/min	100 ± 38 beats/min
Time to symptoms* onset	6.6 ± 4.3 minutes	7.4 ± 3.5 minutes

*In patients who remained asymptomatic during repeat tilt, minimal systolic blood pressure and minimal heart rate recorded during the 15-minute tilt were used for statistical comparison (see Methods).
No significant differences (Student's paired t test).
BP = blood pressure; HR = heart rate.

Reproducibility of time to symptoms: The time to development of symptoms (or maximal decrease in heart rate and systolic blood pressure) varied considerably between patients for both initial and repeat tilt (Figure 3C). No systematic trend for either earlier or later development of symptoms during the repeat tilt was evident.

DISCUSSION

The major finding in this study is that most patients who had an initially positive response to upright tilt testing continued to demonstrate physiologic changes in blood pressure or heart rate when the tilt was repeated under the same conditions. However, ⅓ of patients experience milder symptoms or remained entirely asymptomatic during repeat tilt and were able to remain upright throughout the entire 15 minutes. The timing and extent of the abnormal physiologic response varied con-

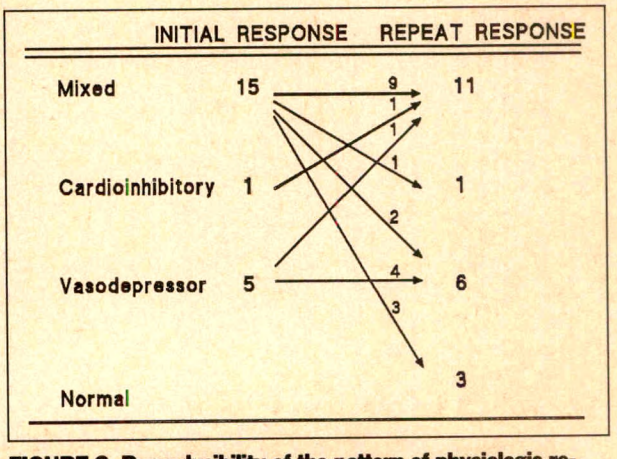


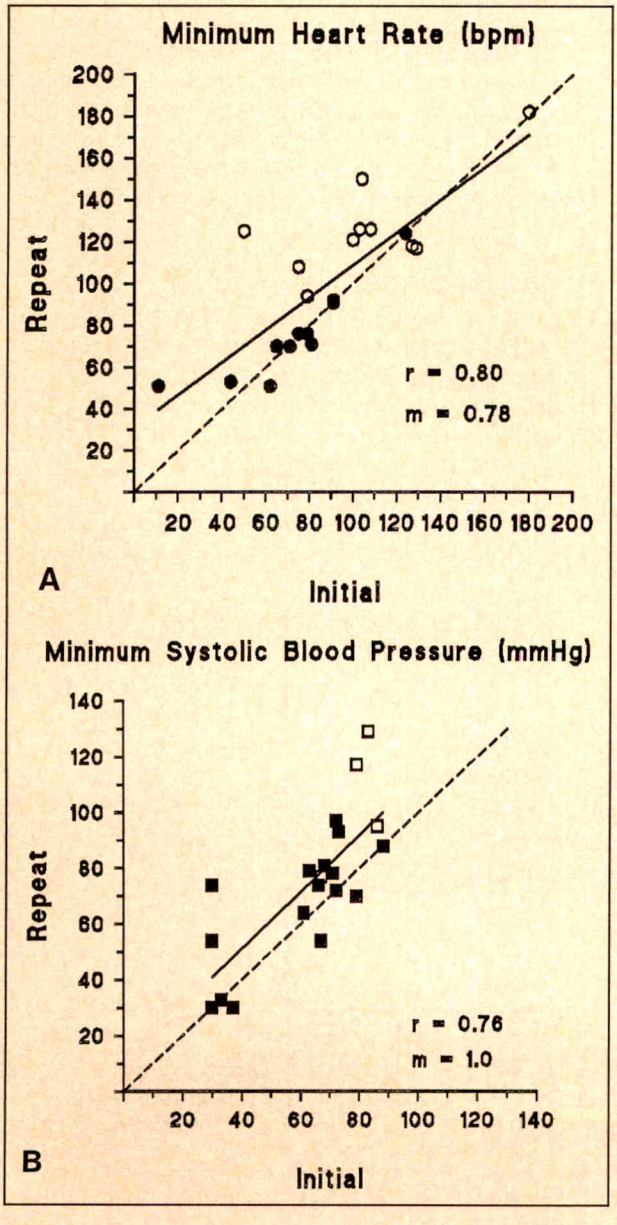
FIGURE 2. Reproducibility of the pattern of physiologic response to upright tilt. Responses during initial tilt are tabulated in the *right column*, all of which resulted in syncope or presyncope (see Figure 1). An identical pattern of response was reproduced in only 13 patients. A different pattern of response was observed in 5 patients, and 3 patients had neither symptoms nor any discernible physiologic response.

siderably for each patient, with an overall trend toward attenuation of both heart rate and blood pressure responses during repeat tilt. Thus, neither subjective features (symptoms) nor objective features (pattern of response, extent of decreases in heart rate or blood pressure, or timing of physiologic changes or symptoms, or a combination of these) appeared to be consistently reproducible from patient to patient. This has important implications regarding assessment of a given person's response to an acute therapeutic intervention.

Head-up tilt testing has been shown to be a valuable investigational and diagnostic tool in evaluating unexplained syncope in ostensibly healthy patients.[3–9] A positive test is thought to result from activation of the Bezold-Jarisch reflex in the development of symptoms[10]; activation of this reflex can elicit 2 separate (but often concurrent) efferent responses: heart rate slowing and peripheral vasodilation. Independently or together, these responses can manifest as 3 possible patterns of physiologic responses: cardioinhibitory response, pure vasodepressor, and mixed (concurrent cardioinhibitory and vasodepressor responses).[4]

Several studies have already used repeated tilt testing to assess treatment efficacy.[1,3,11] Because spontaneous syncopal episodes occur sporadically and unpredictably, such an approach would provide an attractive means of rapidly screening 1 or more treatments under consideration. Likewise, persistent symptoms despite therapy shown to normalize the response to upright tilt may prompt further investigation for other etiologies, rather than switching to an alternative therapy for neurally mediated syncope. However, use of repeat tilt testing for these purposes requires a determination of the reproducibility of the response to upright tilt before the test can be used to assess treatment.

As in previous studies, most patients in this report had decreases in both heart rate and blood pressure in association with symptoms, which we have referred to as a "mixed response." Some investigators have attempted to subdivide patients according to their pattern of response, particularly those with a predominant



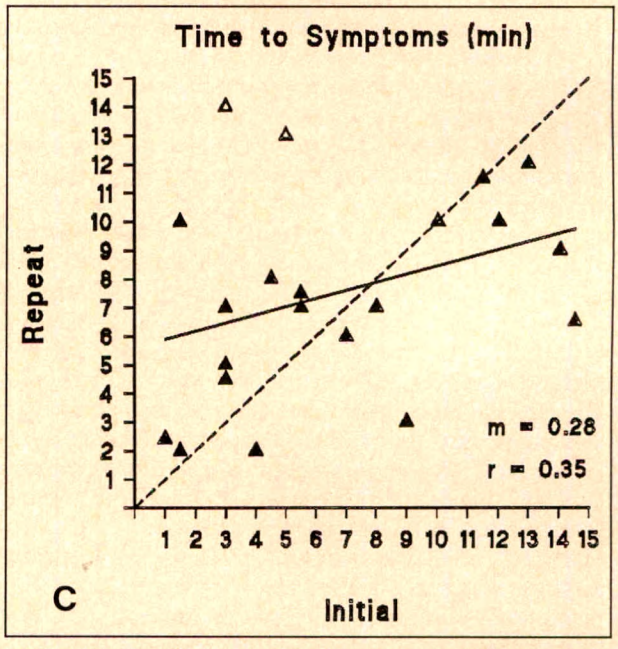


FIGURE 3. Correlation of minimal heart rate, minimal systolic blood pressure, and time to onset of symptoms between initial and repeat tilt. Data during the initial tilt *(horizontal axes)* are plotted against data during repeat tilt *(vertical axes)* for each patient. *A, closed and open circles* indicate patients who did or did not, respectively, manifest a cardioinhibitory component in response to 1 or both tilts. *B, closed and open squares* represent those who did or did not, respectively, experience a vasodepressor component during 1 or both tilts. *C, closed and open triangles* indicate those in whom repeat tilt test did or did not, respectively, elicit a second physiologic response or symptomatic response. In all figures, *solid line* represents the fitted linear regression for all patients, with the corresponding slope (m) and regression coefficient (r) depicted for each graph. Regressions for certain subgroups are included in the text. *Dashed line of identity* is displayed for comparison. Although the group differences (initial versus repeat) were not significant for any of these variables, individual heart rate and blood pressure data tended to lie above the *line of identity*, suggesting an attenuated response to repeat tilt.

cardioinhibitory component.[4,12] It remains uncertain whether such subdivisions are useful. Our data would suggest that patients may have varying predominance of vasodepressor and cardioinhibitory components from 1 symptomatic episode to the next. Both patients with cardioinhibitory responses during 1 tilt had a mixed response during the other tilt. This observation would help account for the frequent failure of pacemaker therapy for patients with syncope due to profound cardioinhibitory responses (sometimes referred to as asystolic arrest).[3,11-13]

Factors influencing response to tilt: The tilt protocol used in this study is similar to protocols used by several other groups studying both young patients and older adults.[3,5,6,9] In a previous study, this protocol elicited symptoms in 80% of young patients undergoing testing for unexplained syncope.[4] Nevertheless, features such as duration and angulation of tilt, and use of isoproterenol may affect the rate of symptomatic responses to tilt testing, and were not examined in this study for possible effects on reproducibility.

Sensitivity and specificity of tilt testing: Differentiation of "false-positive" responses from "true-positive" responses to upright tilt testing is also complicated in that the test presumably identifies a patient's enhanced susceptibility to a "normal" reflex more than an actual pathologic condition. Therefore, the test is unlikely to differentiate previously asymptomatic (yet susceptible) persons from those who have experienced prior episodes. Occasional vasovagal syncope is sufficiently common in adolescents to anticipate a fairly high rate of positive (abnormal) responses among previously asymptomatic but susceptible persons. In both this study and a previous report using this protocol,[4] neurally mediated syncope was highly suspected in all patients studied, based on the history and the initial evaluation. The relative reproducibility of a "negative" tilt session which fails to elicit syncope or presyncope was not examined in this study because of the multiple conditions used. Such an assessment would have required up to 8 periods of tilting (15 minutes each) in a single session.

Implications: The results of the present study are in contrast to various abstracted reports suggesting better correlation between initial and report tilt. The relatively poor correlation in the present report may be attributed to inadequate recovery from the initial symptomatic response. However, the protocol recently described by Fitzpatrick et al,[14] which yielded both high specificity and sensitivity in adults (without the use of isoproterenol), also achieved only 70% agreement with repeat tilt on consecutive days. Thus, wide variability of reproducibility reported for tilt testing protocols reinforces the need for strict definitions of "reproducibility" to be carefully examined before attempting to interpret results of drug testing with repeat tilt.

Repeat tilt testing as performed in this study appears to be highly variable, precluding accurate assessment of acute therapeutic interventions. Furthermore, the trend toward a delayed and frequently attenuated response to repeat tilt would tend to overestimate apparent efficacy of any intervention offered. Whereas placebo-controlled trials of various interventions may demonstrate efficacy among groups of patients, individualized treatment based on acute repeat tilt testing may not be justified. Future attempts to define optimal tilt protocols should include some assessment of reproducibility of the physiologic response if the technique is to be used for drug testing. The variable patterns of physiologic response may also be poorly reproducible, favoring treatments directed at blunting the afferent (triggering) mechanism rather than the efferent response. Absence or recurrence of symptoms continue to be the only reliable end points for treatment efficacy.

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Circadian Rhythm of Heart Rate Variability in Survivors of Cardiac Arrest

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Reduced heart rate (HR) variability is associated with increased risk of cardiac arrest in patients with coronary artery disease. In this study, the power spectral components of HR variability and their circadian pattern in 22 survivors of out-of-hospital cardiac arrest not associated with acute myocardial infarction were compared with those of 22 control patients matched with respect to age, sex, previous myocardial infarction, ejection fraction and number of diseased coronary arteries. Survivors of cardiac arrest had significantly lower 24-hour average standard deviation of RR intervals than control patients (29 ± 10 vs 51 ± 15 ms, $p < 0.001$), and the 24-hour mean high frequency spectral area was also lower in survivors of cardiac arrest than in control patients (13 ± 7 $ms^2 \times 10$ vs 28 ± 14 $ms^2 \times 10$, $p < 0.01$). In a single cosinor analysis, a significant circadian rhythm of HR variability was observed in both groups with the acrophase of standard deviation of RR intervals and high-frequency spectral area occurring between 3 and 6 A.M. which was followed by an abrupt decrease in HR variability after arousal. The amplitude of the circadian rhythm of HR variability did not differ between the groups.

Thus, HR variability is reduced in survivors of cardiac arrest but its circadian rhythm is maintained so that a very low HR variability is observed in the morning after awakening, corresponding to the time period at which the incidence of sudden cardiac death is highest.

(Am J Cardiol 1992;70:610–615)

From the Division of Cardiology, Department of Medicine, Oulu University Central Hospital, Oulu, Finland; and Miami University Medical Center, Miami, Florida. This study was supported by a grant from the Finnish Foundation for Cardiovascular Research, Helsinki, Finland; Grant HL28130 from the National Heart, Lung, and Blood Institute, Bethesda, Maryland; and Grant IF05W04022-01 from the Fogarty International Foundation, Washington, D.C. Manuscript received January 31, 1992; revised manuscript received and accepted May 18, 1992.

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Recent studies have demonstrated that decreased heart rate (HR) variability is a predictor of sudden cardiac death in patients with coronary artery disease.[1,2] Studies on normal healthy subjects and patients without evidence of organic heart disease have shown that HR variability exhibits a circadian rhythm with the lowest values in the morning hours after awakening.[3,4] Sudden cardiac death also has a circadian pattern with the highest incidence between 7 and 11 A.M.[5] The increased frequency of cardiac deaths in the morning hours has largely been attributed to increased density of ischemic episodes after arousal in the morning. Little information has been available on the possible circadian rhythm of HR variability in high-risk patients with coronary artery disease and on the possible contribution of circadian fluctuation of cardiac autonomic function to fatal cardiac events. The aim of this study was to compare the circadian rhythm of standard deviation of RR intervals and spectral components of HR variability between survivors of cardiac arrest not associated with acute myocardial infarction and control patients without history of malignant arrhythmia who were matched for factors that may influence the magnitude of HR variability.[6–11]

METHODS

Survivors of cardiac arrest: Twenty-two consecutive patients who were successfully resuscitated from out-of-hospital cardiac arrest (6 in Miami University Medical Center, and 16 in Oulu University Central Hospital between August 1988 and April 1990) not associated with acute myocardial infarction were included in the study. Myocardial infarction was ruled out by serial creatine kinase-MB fraction measurements and absence of new Q waves on an electrocardiogram. Patients with clinical evidence of central nervous system damage, congestive heart failure, sinus node dysfunction, atrial fibrillation or frequent ectopic beats (>100 ventricular ectopic beats/hour) at the time of 24-hour electrocardiographic recordings were excluded. The 24-hour electrocardiographic recordings were performed at a mean of 6 ± 4 days (range 1 to 12) after cardiac arrest when the patients were ambulatory and having their normal sleeping and awake rhythms.

All patients underwent left-sided cardiac catheterization including left ventricular cineangiogram and selective coronary angiograms. The clinical data of the patients are summarized in Table I.

Control patients: The control group was selected from among the patients who were referred to angiographic studies because of angina pectoris or for prog-

nostic reasons in Oulu University Central Hospital. The control patients and survivors of cardiac arrest were matched with respect to age, sex, previous myocardial infarction, left ventricular ejection fraction and number of diseased coronary arteries. The matched parameters were dichotomized as follows: (1) age < or >60 years; (2) male or female gender; (3) presence or absence of prior Q-wave myocardial infarction; (4) left ventricular ejection fraction <30%, between 30% and 50% or >50%; and (5) 1-vessel, 2-vessel, or 3-vessel coronary artery disease on angiography. A patient in the control group was matched with a survivor of cardiac arrest for at least 4 of the 5 variables. The matching was performed before analyses of 24-hour electrocardiographic recordings. The clinical data of the control group are summarized in Table I. All control patients underwent left-sided cardiac catheterization including the angiographic studies.

The 24-hour electrocardiographic recordings were performed in the hospital in all patients before cardiac catheterization studies. Beta-blocking and antiarrhythmic drugs were withdrawn at least 5 half-lives beforehand in all patients. Each patient gave informed consent for the studies.

Invasive studies: Left-sided cardiac catheterization was performed by the Judkins' technique. Left ventricular cineangiograms were recorded in the 45° right anterior oblique projection and the ejection fraction was calculated as a single-plane area-length method. Coronary artery stenoses with >50% luminal narrowing were considered significant.

Ambulatory electrocardiographic recordings: All patients underwent a 24-hour electrocardiographic recording. Two-channel 24-hour electrocardiographic recordings were analyzed by a Delmar Avionics scanner. The number of ventricular ectopic beats, episodes of repetitive ectopic beats and episodes of ventricular tachycardia were analyzed from the tape recordings.

Analysis of heart rate variability: The digitally sampled electrocardiographic data were transferred from the Delmar Avionics scanner to a microcomputer for analysis of HR variability. A linear detrend was applied to the RR interval data in segments of 512 samples to make it more stationary. This was implemented by first fitting a straight line to a segment by a standard least-squares method and then subtracting it from the sample values. The computer program labels each QRS complex, and the RR interval series is passed through a filter that eliminates ectopic beats and artifacts and fills the resulting gaps with an average value computed in the local neighborhood. In addition, the RR intervals were reviewed on the computer display by an experienced observer, and only those RR intervals related to normal sinus beats in a stationary state were included in the final analysis. Segments that qualified for ≥90% of the RR intervals were included.

An autoregressive model was used to estimate the power spectral densities of the RR interval variability.[12] The size of 10 was used for the model order in the analysis of the RR data.[13,14] The computer program calculates the autoregressive coefficients to define the power spectral density. Power spectra were quantified by measuring the area in 2 frequency bands: low-frequency power (0.04 to 0.15 Hz), and high-frequency power (0.15 to 0.40 Hz). The average RR interval and the standard deviation of the mean RR interval measured from successive 5-minute periods were also calculated. The average HR, standard deviation of RR intervals, and low- and high-frequency spectral areas were calculated for each 1-hour period and for the 24-hour period in each patient.

TABLE I Clinical and Angiographic Characteristics of Patients

	Survivors of Cardiac Arrest (n = 22)	Control Patients (n = 22)
Clinical data		
Age (years)	59 ± 8	60 ± 7
Sex (women/men)	4/18	4/18
History of congestive heart failure	4 (18%)	5 (23%)
Cardiac medication		
Digitalis	11 (50%)	5 (23%)
Diuretic	14 (64%)	7 (32%)
Nitrate	14 (64%)	19 (86%)
Calcium antagonist	4 (18%)	11 (50%)
ACE inhibitor	3 (14%)	3 (14%)
Previous myocardial infarction		
None	2 (9%)	2 (9%)
Anterior	10 (45%)	10 (45%)
Inferior	7 (32%)	7 (32%)
Anterior+inferior	3 (14%)	3 (14%)
Electrocardiogram		
Q waves	17 (77%)	18 (82%)
Intraventricular conduction defect	5 (23%)	2 (9%)
New York Heart Association functional class		
1	3 (14%)	2 (9%)
2	11 (50%)	11 (50%)
3	6 (27%)	8 (36%)
4	2 (9%)	1 (5%)
Time of cardiac arrest (n = 20)		
Bet. 12 P.M. and 6 A.M.	1 (6%)	
Bet. 6 A.M. and 12 A.M.	9 (39%)	
Bet. 12 A.M. and 6 P.M.	6 (33%)	
Bet. 6 P.M. and 12 P.M.	4 (22%)	
Angiographic data		
Ejection fraction (%)	40 ± 16	44 ± 15
Coronary angiography		
1-vessel disease	5 (23%)	3 (14%)
2-vessel disease	9 (41%)	9 (41%)
3-vessel disease	8 (36%)	10 (45%)

ACE = angiotensin-converting enzyme; Bet. = between.

Statistics: Spectral areas, average HR and standard deviation of RR intervals were compared between survivors of cardiac arrest and control patients with the unpaired Student's *t* test. A p value <0.05 was considered significant. Data between the groups were compared with chi-square test or Fisher's exact test. The chronobiologic analysis of the mean hourly values of parameters of HR variability was made by single cosinor method,[15] in which a least-squares procedure is used and a cosine function is fitted to the data. Three parameters characterize this model: mesor, a rhythm-determined average; amplitude, one-half difference between the highest and lowest values in a rhythm defined by the

TABLE II Ventricular Arrhythmias on 24-Hour Electrocardiographic Recordings

	Survivors of Cardiac Arrest (n = 22)	Control Patients (n = 22)
No. of VPCs		
None	2 (9%)	7 (29%)
1–30/hour	14 (64%)	14 (64%)
30–100/hour	6 (27%)	1 (5%)
Repetitive VPCs (2–5)	7 (32%)	0 (4%)
Nonsustained VT (>5 beats)	6 (27%)	0 (4%)

VPCs = ventricular premature complexes; VT = ventricular tachycardia.

TABLE III Twenty-Four-Hour Average Heart Rate Variability

	Survivors of Cardiac Arrest (n = 22)	Control Patients (n = 22)
SD of RR intervals (ms)	29 ± 10	51 ± 15*
High-frequency spectral area ($ms^2 \times 10$)	13 ± 7	28 ± 14†
Low-frequency spectral area ($ms^2 \times 10$)	14 ± 13	22 ± 12
Ratio between low- and high-frequency areas	1.2 ± 0.9	0.9 ± 0.3

*$p < 0.001$; †$p < 0.01$ between the groups.

cosine function; and acrophase, the lag from a reference time point (midnight) and time of the highest value in the cosine model fitted to the data. The 95% confidence interval of the mesor and amplitude of parameters of HR variability were calculated for both patient groups.

RESULTS

Clinical and angiographic data: The clinical and angiographic data of both patient groups are summarized in Table I. Ventricular fibrillation was the presenting arrhythmia at the time of cardiac arrest in 15 patients, fast ventricular tachycardia in 6, and the presenting arrhythmia in 3 patients was not documented. Ventricular arrhythmias detected on 24-hour electrocardiographic recordings are presented in Table II.

Heart rate variability: The average 24-hour standard deviation of RR intervals and high-frequency spectral area were significantly lower in survivors of cardiac arrest than in control patients (Table III). The low-frequency spectral area and the ratio between low- and high-frequency spectral areas did not differ significantly between the groups. Although mean values differed, there was some overlapping in the individual measurements of HR variability between the groups (Figure 1).

Circadian rhythm of heart rate variability: The standard deviation of RR intervals and high-frequency spectral area showed circadian variation in both groups (Figures 2 and 3, Table IV). The acrophase of both standard deviation of RR intervals and high-frequency spectral area occurred during the sleeping hours just before arousal. The acrophase was followed by an abrupt decrease in standard deviation and high-frequency spectral component in the morning after awakening in both patient groups. No significant differences were detected in the amplitude of circadian rhythms of HR between the groups. Examples of 1 cardiac arrest patient and 1 control patient are presented in Figures 4 and 5.

DISCUSSION

Heart rate variability in survivors of cardiac arrest: Twenty-four-hour average standard deviation of RR intervals and high-frequency spectral area of HR variability were reduced in survivors of cardiac arrest compared with that of matched control patients. Two previous studies have estimated HR variability in patients with cardiac arrest. Martin et al[16] reported on 5 patients with cardiac arrest during ambulatory electrocardiographic recording who had significantly lower standard deviation of RR intervals than normal control subjects without heart disease. Myers et al[17] compared power spectra of HR variability, analyzed by the fast-Fourier transform method, among 6 patients resuscitated from cardiac arrest and 6 patients with cardiac disease and also found that HR variability was reduced in patients

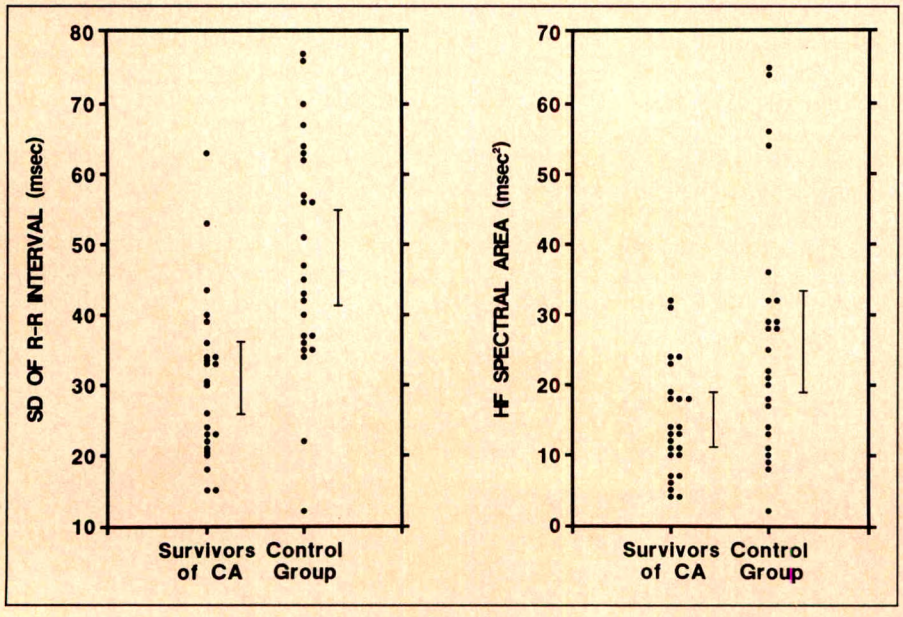


FIGURE 1. Individual values of standard deviation (SD) of RR (R-R) intervals and high-frequency (HF) power spectra of heart rate variability and 95% confidence intervals of the mean values *(bars)* in survivors of cardiac arrest (CA) and in control patients.

with cardiac arrest. Neither of these previous studies with rather small numbers of patients matched their control patients with respect to age and severity of coronary artery disease, which may influence the magnitude of HR variability.[9]

Time domain measures of HR variability have been previously used to assess the risk of death in patients with coronary artery disease.[1,2] However, evaluation of frequency domain of RR intervals (spectrum analysis) offers distinct advantages to study autonomic function in heart disease.[18–20] A possible major advantage of spectral analysis is that parasympathetic and sympathetic activity can be separately quantified. In this study we observed that the high-frequency spectral area of HR variability was more reduced in survivors of cardiac arrest, and that the low-frequency spectral component did not discriminate between the groups, suggesting that vagal HR control is impaired in survivors of cardiac arrest.

Several possible factors may influence HR variability in high-risk patients, including advanced age, previous myocardial infarction, severity of coronary artery disease, impaired left ventricular function, congestive heart failure, cardiac medication, central nervous sys-

TABLE IV Single Cosinor Analysis of Circadian Rhythms of Heart Rate and Heart Rate Variability

	Survivors of Cardiac Arrest (n = 22)	Control Patients (n = 22)
HR (beats/min)		
Mesor	69 (68–70.0)	67 (66–69)
Amplitude	4 (2–5)	7 (5–9)
Acrophase	2.00 P.M.	10.30 A.M.
SD of RR intervals (ms)		
Mesor	29 (27–31)	51 (48–54)
Amplitude	2 (0–4)	3 (1–5)
Acrophase	5.30 A.M.	5.00 A.M.
LF spectral area ($ms^2 \times 10$)		
Mesor	14 (9–19)	22 (17–27)
Amplitude	4 (−1–9)	2 (−2–6)
Acrophase	6.30 A.M.	9.00 A.M.
HF spectral area ($ms^2 \times 10$)		
Mesor	13 (10–16)	28 (24–32)
Amplitude	3 (1–5)	4 (1–7)
Acrophase	3.30 A.M.	3.45 A.M.
LF/HF ratio		
Mesor	1.2 (0.9–1.5)	0.8 (0.6–1.1)
Amplitude	1 (−1–3)	0 (−2–2)
Acrophase	4.00 P.M.	11.00 A.M.

Parentheses indicate 95% confidence intervals.
HR = heart rate; LF = low-frequency; HF = high-frequency.

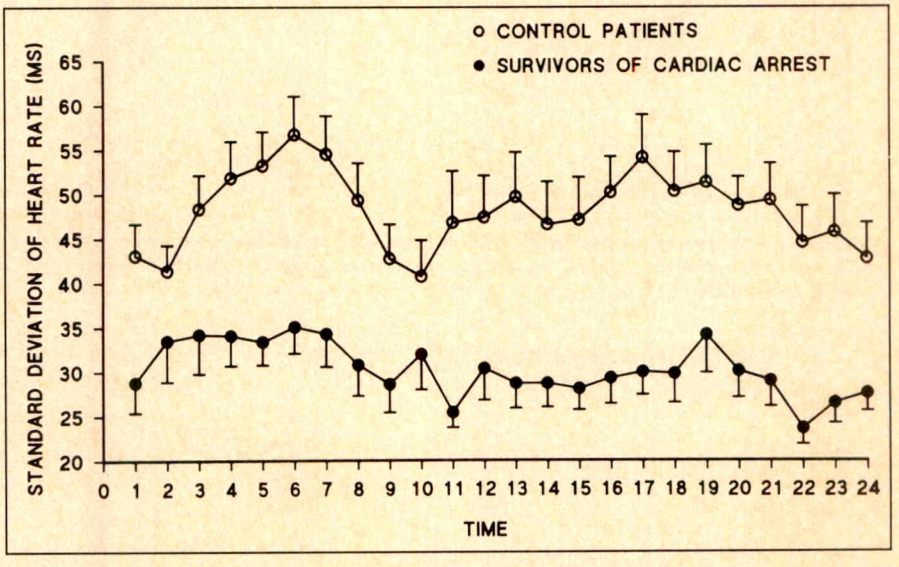


FIGURE 2. Circadian rhythm of mean (± SEM) values of standard deviation of RR intervals in survivors of cardiac arrest and matched control patients.

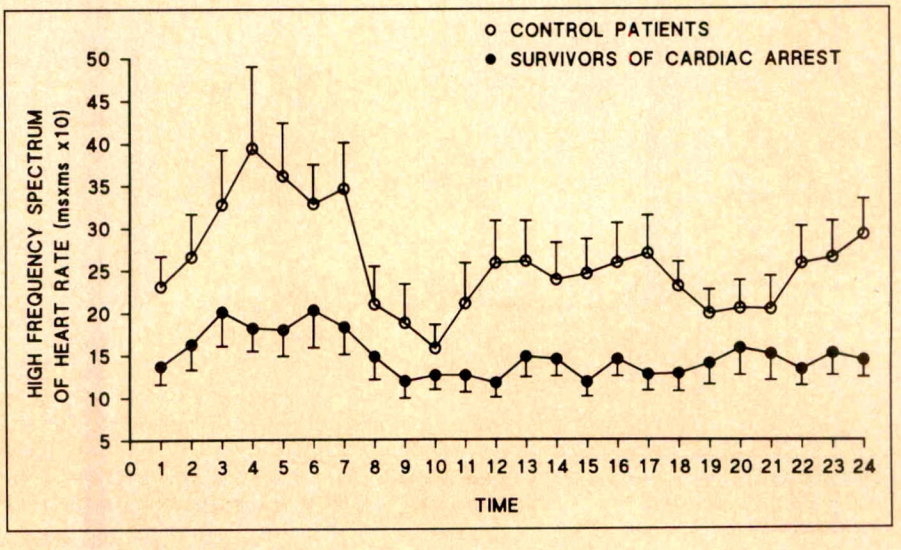


FIGURE 3. Circadian rhythm of mean (± SEM) values of high-frequency spectral area of heart rate variability in survivors of cardiac arrest and matched control patients.

tem damage, physical inactivity, impairment of sinoatrial node, and ischemic damage of the intrinsic cardiac nerves or cardiac receptors, or both.[6–11] The 2 groups in this study were matched with respect to age, clinical characteristics and severity of underlying coronary artery disease. Differences in physical activity at the time of the recordings cannot explain the reduced vagal activity in patients with cardiac arrest, because the differences in HR variability between the groups were greatest during sleep in the early morning hours. We cannot exclude subclinical ischemic damage to the central nervous system as a causative factor for reduced HR variability in cardiac arrest survivors. However, 1 previous study suggested that regardless of type of central ner-

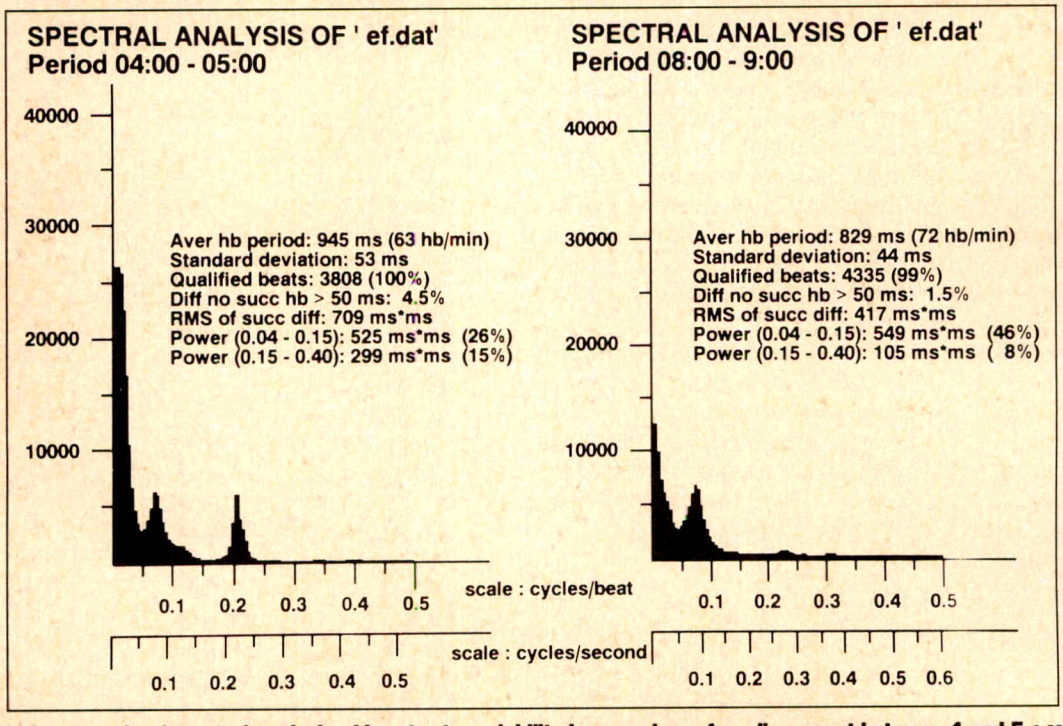


FIGURE 4. An example of spectral analysis of heart rate variability in a survivor of cardiac arrest between 4 and 5 A.M. *(left)*, and between 8 and 9 A.M. *(right)*. Significant reduction is observed in the high-frequency spectral area in the morning after arousal. Diff = difference; hb = heart beat; RMS = root-mean square; succ = successive.

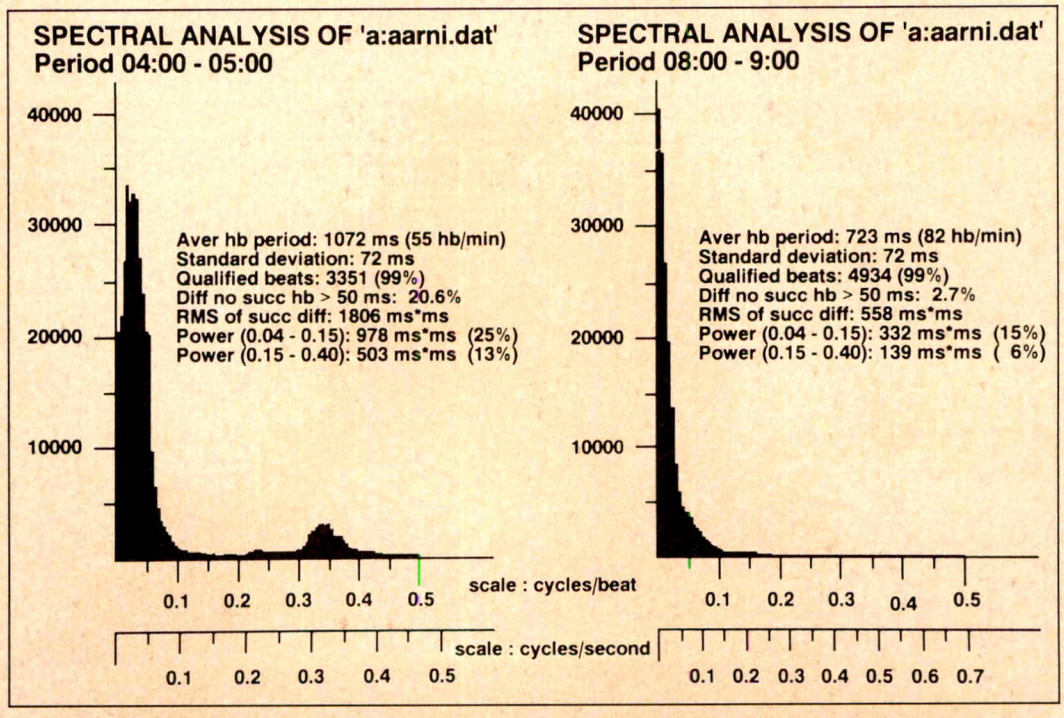


FIGURE 5. An example of spectral analysis of heart rate variability in a control patient between 4 and 5 A.M. *(left)*, and between 8 and 9 A.M. *(right)*. Both low- and high-frequency spectral areas are markedly reduced in the morning after arousal in this patient. Abbreviations as in Figure 4.

vous system lesion, a typical pattern of respiratory sinus arrhythmia remained intact.[21] Further studies using different methods are needed to distinguish between changes in efferent neural activities or target function responsiveness as causative factors for impaired HR variability in survivors of cardiac arrest.

Circadian rhythm of heart rate variability: A distinct reproducible circadian pattern of HR variability was observed in both patient groups, with the acrophase occurring in the morning hours before arousal. This was followed by an abrupt decrease in HR variability after arousal, resulting in very low vagal HR control in survivors of cardiac arrest in the morning. To our knowledge, no information has been previously available about the possible circadian rhythm of cardiac autonomic function in high-risk patients with coronary artery disease. We have previously reported a similar circadian rhythm of HR variability in normal healthy subjects.[3] Furlan et al[4] demonstrated a rapid increase in sympathetic activity and concomitant vagal withdrawal both in hospitalized and nonhospitalized patients without evident heart disease. High values of circulating plasma catecholamine levels have also been observed in the morning.[22] These data support the view that autonomic imbalance should be considered as a potential contributory factor for increased prevalence of sudden cardiac death during the morning hours.

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Use of Telemetry Functions in the Assessment of Implanted Antitachycardia Device Efficacy

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Twenty patients (aged 50 ± 21 years and mean left ventricular ejection fraction 37 ± 17%) with recurrent ventricular arrhythmias were treated with an investigational, implantable combined antitachycardia-pacing cardioverter defibrillator. The device's telemetry capabilities include both stored (1-second snapshots) and real-time display of endocardial and device-circuit signals. The device can store these before, during and after up to 50 tachycardia and antitachycardia pacing episodes. All stored events are indexed to a 24-hour internal clock. During 10.1 ± 5.1 months of follow-up, the device was used in 11 of 20 patients. In the entire group, antitachycardia pacing was activated on 44 ± 14 occasions per patient (total 874) and shock delivery occurred on 8 ± 14 occasions per patient (total 156). Reconstruction by stored telemetry of all device-therapy episodes was possible. Twenty-six percent of all shocks delivered were not appropriate and were due to atrial arrhythmias in 2 patients and dysfunction of the sensing lead in 3. The absence of a relation between symptoms and appropriate shock delivery was documented in 1 patient. Antitachycardia pace acceleration occurred in 5.3% of cases; 7% of attempts at pacing were unsuccessful and needed shock therapy. It is concluded that the enhanced telemetry available in newer antitachycardia devices enables more accurate assessment of device use and enhances diagnosis of inappropriate therapy delivery.

(Am J Cardiol 1992;70:616–621)

Unlike currently approved devices that are limited to direct-current shock only, investigational implanted defibrillators have a hierarchy of therapies, ranging from antitachycardia pacing to low-energy cardioversion to high-energy direct-current shock, which can be adapted to each patient's need.[1] Together with advances in therapy, sophisticated telemetry capabilities are available in real time and from data collected and stored at the time of therapy delivery. This can provide reconstruction of the events leading to device activation, together with correlation of symptoms with events. Information other than symptoms can then be used in the assessment of device efficacy and may provide insight to the evaluation of device use and function in the ambulatory setting. This simplifies patient follow-up and enables evaluation of the effects of antitachycardia pacing and reprogramming on device efficacy in the true clinical environment. We report on a series of 20 patients with a device that provides telemetered display of stored or real-time events and device function.[2] Our purpose was to assess the impact of memory and telemetry functions on clinical device use and follow-up.

METHODS

Device: The device used in all patients was a Guardian model 4210 implanted defibrillator (Telectronics Pacing Systems, Sydney, Australia). This device delivers a monophasic, truncated, exponentially decaying, defibrillatory shock and uses 2 screw-in epicardial leads or a transvenous endocardial lead for sensing and antitachycardia pacing. At a programmable tachycardia detection interval, the device first detects then confirms the presence of a tachycardia using a programmable algorithm. As illustrated from a real-time record of an induced arrhythmia (Figure 1), the beginning of the sinusoidal line on the logic-circuitry channel indicates that detection and subsequent confirmation of a tachycardia have occurred. If the tachycardia rate is within a specified, programmable range, the first train of antitachycardia pacing (adapted to the tachycardia cycle length) is delivered; if unsuccessful, successively faster pacing trains are delivered until tachycardia terminates, the rate accelerates to exceed a specified rate, or a programmed number of attempts of pace termination are delivered. If a heart rate exceeding the detection interval is still present, the device progresses to cardioversion or defibrillation at programmable energies in a user-defined sequence. At rates higher than the programmed

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range for antitachycardia pacing, only shocks are delivered.

The antitachycardia pacing functions of the device allow for a scanning burst in a fixed or adaptive (i.e., as a function of tachycardia cycle length) mode, with programmable first and succeeding coupling intervals, the number of beats in a train, the number of attempts, and the shortest pacing cycle length permitted. The pacing cycle length progressively shortens in a programmable fashion between successive bursts.

The device can store up to 50 separate tachycardia episodes. These are referenced to an internal real-time clock with the availability of concomitant 1-second "snap shots" of both endocardial and logic-circuitry signals; these are available at the time of initial tachycardia detection, progression from antitachycardia pacing to shock therapy, and after therapy. Detailed data logs of the date, time and 32 RR intervals preceding each detection of tachycardia, as well as all subsequent intervals during therapy episodes (including confirmation and after therapy) are available. The device can provide a summary of the time and outcome of all tachycardia and fibrillation detections.

Patient selection: All patients with either recurrent ventricular tachycardia or fibrillation needing an implanted antitachycardia device at a University of Toronto teaching hospital (St. Michael's Hospital, Hospital for Sick Children or the Toronto Hospital) were eligible for the study. The indications for implantation were left to the discretion of the individual investigators. All patients gave informed consent for participation in an investigational device protocol that was approved by the University of Toronto human subjects review committee. Patients were followed up at 2-month intervals in the implantable defibrillator clinic. Devices were interrogated, and therapy that had been delivered was assessed at each visit.

RESULTS

Twenty patients (age range 10 to 70 years, mean 50 ± 21) received devices between December 1989 and September 1991. Thirteen patients had coronary artery disease; the remainder had idiopathic dilated cardiomyopathy (n = 2), primary electrical disease (n = 1) and nonobstructive hypertrophic cardiomyopathy (n = 4). The presenting arrhythmia was ventricular fibrillation in 7 patients and poorly tolerated ventricular tachycardia in the other 13, with a mean VT cycle length of 368 ± 69 ms. Patients experienced 2.1 ± 2.0 arrhythmia episodes before implantation, despite treatment with 2.3 ± 1.5 antiarrhythmic agents, including amiodarone in 12 patients (60%). Mean left ventricular ejection fraction was 37 ± 17%, as determined by nuclear angiography.

Intraoperative testing: Defibrillation thresholds were tested intraoperatively; the lowest successful energy for defibrillation was 21.4 ± 8.7 J. Epicardial screw-in leads were placed in 14 patients. Mean R-wave amplitude in sinus rhythm was 11.1 ± 5.6 mV.

Intracardiac signals together with the timing event marker and surface electrocardiographic signals were displayed during the induction of ventricular fibrillation; the devices were tested in the automatic mode and functioned appropriately in all cases.

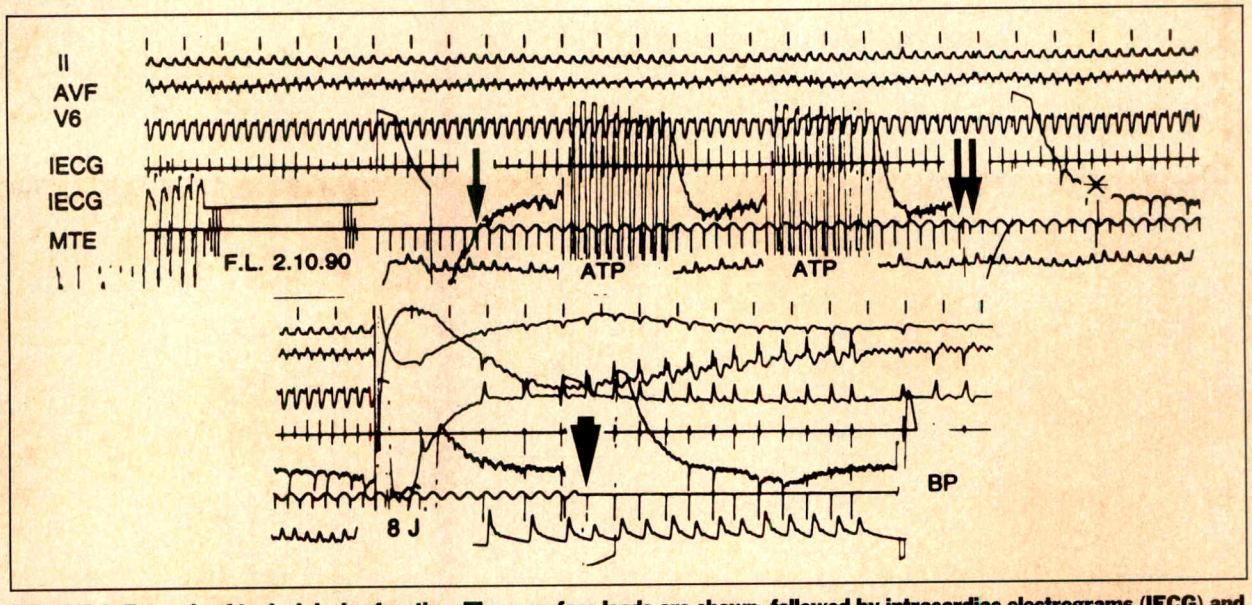


FIGURE 1. Example of typical device function. Three surface leads are shown, followed by intracardiac electrograms (IECG) and main timing event marker (MTE). After induction of ventricular tachycardia (cycle length 320 ms, 188 beats/min), device is activated. After 8 sensed beats, onset of wavy line on event marker *(first arrow)* indicates that rhythm is within tachycardia detect interval. After a further 8 beats of tachycardia, reconfirmation is complete, and first of 2 bursts of antitachycardia pacing (ATP) is delivered at 90 and 80% of tachycardia cycle length. These do not affect tachycardia, and (as indicated at *double arrow* on timing event channel) amplitude of spikes decreased, indicating change to shock mode with automatic doubling of sensitivity threshold of sensing circuitry. This is followed by charging onset indicator *(star)* and subsequent delivery of 8 J cardioverting shock with restoration to sinus rhythm. After shock *(arrowhead)*, timing channel indicates sensed rhythm outside programmed detect interval. Device also has available backup bradycardia support functions not needed in this example. Timing event signal in this example is derived from real-time telemetry. Same signal and markers are available from stored data, together with intracardiac electrogram signal in 1-second snapshots. BP = radial artery blood pressure.

TABLE I Clinical Follow-Up

Pt.	Antitachycardia Pacing*	Shock Delivery*	Lead Revision	Reprogram†	Outcome
1	0	0			A
2	0	0			A
3	0	2	+		A
4	0	0			A
5	18	1			A
6	2	6		+	A
7	3	36		+	A
8	290	51			T
9	0	0			A
10	0	0			A
11	0	0			A
12	0	1	+		D
13	32	15		+	T
14	26	6	+		A
15	20	30		+	D
16	2	0			A
17	481	8			T
18	0	0			A
19	0	0			A
20	0	0			A
Mean ± SD	44 ± 121	8 ± 14			

*Number of episodes of antitachycardia pacing or shock delivery during follow-up of 10 ± 5 months.
†Change in tachycardia detect interval (patients 6 and 12); disabled antitachycardia pacing (patients 13 and 15).
A = alive; D = deceased; T = cardiac transplantation.

All patients had epicardial patches implanted. The patches were a combination of small (area 15 cm^2), medium (28 cm^2) or large (40 cm^2). Only 1 patient received 2 small patches. All patients left the operating room with antitachycardia functions disabled and defibrillation therapy enabled. There were no intraoperative complications. One patient undergoing device replacement developed wound infection at the generator site within 30 days after surgery. Cultures from the pulse generator pocket grew S epidermidis. The patient's device and all leads were explanted.

Electrophysiologic studies before discharge: Studies were performed 5 to 7 days after surgery. Ventricular tachycardia could be initiated in 13 patients. All patients with ventricular tachycardia began therapy with antitachycardia pacing in an adaptive mode, beginning with a 90% interval between the last tachycardia beat and the first paced beat, with a subsequent 8- to 12-beat burst beginning at 90% of the tachycardia cycle length. With each repeat burst the antitachycardia pacing cycle length decreased, down to 70% of the original tachycardia rate over 3 to 5 attempts. The minimum antitachycardia burst pacing cycle length was set no lower than 230 ms (261 beats/min). At testing before discharge, 26 episodes of induced ventricular tachycardia were treated with pacing therapy in 10 patients. Antitachycardia pacing was successful in 24 of 26 episodes, need-

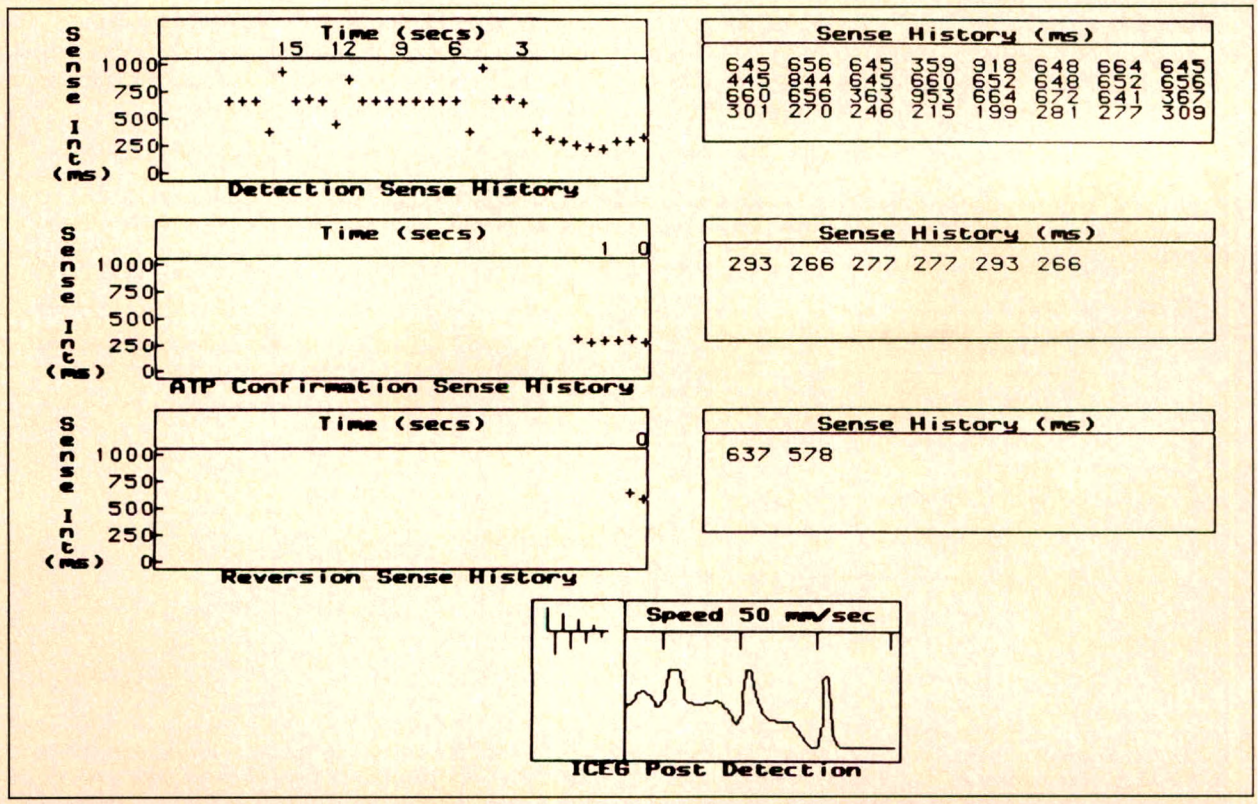


FIGURE 2. Example of original data available on interrogation during outpatient follow-up. Both actual RR intervals (Int) (*right panels*) and graph of RR intervals (*left panels*) are available for analysis, together with stored intracardiac electrogram (ICEG) and timing event signal (in this case only requested for the time of confirmation before therapy delivery). At 09:37, the patient had an episode of ventricular tachycardia that the device sensed at a calculated average cycle length of 279 ms (215 beats/min). Telemetry revealed 1 episode of antitachycardia pacing (8 beats, 90% of tachycardia cycle length) that was followed by prompt reversion. The entire episode of sense, confirmation and delivery of therapy lasted 8 seconds and was accompanied by palpitation. See text for further details. ATP = antitachycardia pacing.

ing 2.1 ± 1.3 (range 1 to 5) successive pace termination attempts per induced tachycardia episode. Two induced tachycardia episodes were successfully treated with a cardioverting shock after 5 unsuccessful pace termination attempts. Nine episodes of induced ventricular fibrillation were terminated on the first shock in 9 patients.

Follow-up (Table I): Patients were followed up for 10.1 ± 5.1 months (range 1 to 17). All devices functioned according to specifications, with no sudden battery depletion, device inactivation or malfunction. Actuarial survival was 86% at 12 months. Four patients were censored at the time of heart transplant (n = 3) or device removal (n = 1), and 2 deaths were due to electromechanical dissociation. During follow-up, the device delivered therapy to 11 patients with antitachycardia pacing used an average of 44 ± 121 times; 156 shocks (range 1 to 36) were delivered to 10 patients.

Analysis of RR intervals and stored signals prior to, during and after episodes of therapy delivery enabled determination of the appropriateness of shock delivery. Of 874 pace termination attempts (90% occurring out of the hospital), acceleration led to shock delivery in 5.3%; and another 7% of patients received shock therapy after unsuccessful successive pace termination attempts.

Telemetry of recorded episodes enabled reconstruction of the RR intervals surrounding therapy in all cases. Figure 2 shows an example from the original data of an episode of successful pace termination. The RR intervals are printed and displayed graphically from the time of event detection, confirmation before antitachycardia pacing and after delivery of a 10-beat adaptive burst at 80% of the tachycardia cycle length. The tachycardia rate was unstable and averaged 279 ms (215 beats/min). The stored intracardiac and simultaneous logic-circuit signal after detection is also displayed.

Not all episodes of appropriate device function were symptomatic. Table II summarizes the telemetry record of RR intervals from an episode of ventricular tachycardia. At 0 second, ventricular tachycardia was detected at a cycle length of 490 ms (122 beats/min). After confirmation, 12 pulses at 90% of the ventricular tachycardia cycle length were delivered. The tachycardia was confirmed to be unaltered, and further pacing attempts continued at 85, 80, 75 and, again, 90% of the tachycardia cycle length. At the end of the programmed number of pace termination attempts, the tachycardia was accelerated to 190 beats/min (350 ms). After further confirmation, a 25 J shock was delivered at 52 seconds. This did not terminate the tachycardia, but instead accelerated the rate to 275 ms (218 beats/min) at 57 seconds into the episode. For the next 10 seconds, while the device charged its capacitor, this rhythm degenerated to ventricular fibrillation (cycle length 145 to 115 ms), after which a second shock of 37.9 J was delivered (60 seconds after the beginning of ventricular tachycardia) with reversion to sinus rhythm. The patient was conscious and unaware of antitachycardia pacing until just before shock delivery.

Forty-one shocks (26%) delivered were thought to have been inappropriate to the clinical situation. Thirty-six shocks were due to documented sinus or atrial tachyarrhythmias initiating device-sensed events in 2 patients. Three patients received 5 shocks because of a loss of integrity of the lead system based on analysis of telemetered data, which was subsequently confirmed at surgery. The absence of symptoms before shock delivery, together with the finding of frequent ventricular fibrillation detections with spontaneous reversion, was an important clue to the presence of possible spurious tachycardia detection due to a lead fracture. This could be confirmed by analysis of the signals stored at the time of shock delivery, which demonstrated a discordance between the timing event signal and the intracardiac electrogram owing to the generation of multiple "make-break" potentials from the disrupted lead.

TABLE II Reconstruction of an Episode of Tachycardia*

Time (sec)	Cycle Length (ms)	Intervention
0	490	Tachycardia detection
4	490	ATP #1; 90% VT CL
11	350	ATP #2; 85% VT CL
19	465	ATP #3; 80% VT CL
26	365	ATP #4; 75% VT CL
31	300	ATP #5; 90% VT CL
40	315	Reconfirm and charge capacitors
52	320	Deliver 25 J DC shock
57	275	Reconfirm and charge capacitors
67	115–300	Deliver 37.9 J DC shock
72	615	Confirm reversion to sinus

*As determined from telemetry log entries of RR intervals used for detection and reconfirmation and during delivery of therapy in patient 8 (see text for further details).
ATP = antitachycardia pacing trains, all delivered in adaptive scanning mode with first paced coupling interval of 90%, followed by 11 beats of pacing at indicated percentage of ventricular tachycardia cycle length (VT CL); DC = direct-current.

This is illustrated in Figure 3 (left panel), which shows telemetry of a stored endocardial signal with the simultaneously stored logic-circuit signal from such a patient obtained at the time of a follow-up clinic visit. This shows 1 QRS complex during the 1-second interval with simultaneous multiple endocardial activations detected (recorded as events on the main timing circuit channel). At assessment (Figure 3, middle panel), manual movement of the pulse generator while recording the same simultaneous signals confirmed the presence of multiple make-break potentials that at surgical exploration were found to be due to a lead fracture. Many of the 32 RR intervals before tachycardia detection (onset of wavy line; Figure 3, right panel) were the nonphysiologic RR intervals and triggered tachycardia detection; although this led to frequent spurious detections of ventricular fibrillation, it did not result in shock delivery, because the "noncommitted" algorithm of the device confirms the presence of ventricular fibrillation (during the charging sequence) before shock and holds the charge on the capacitors if spontaneous reversion occurs.

During follow-up, reprogramming was performed in 4 patients. In 2 patients, this was performed to change the tachycardia detection interval, because of rapid atrial arrhythmias occurring after implantation. In another 2 patients with well-tolerated ventricular tachycardia at rates of 100 to 120 beats/minute, pace acceleration to a

poorly tolerated rhythm led to a disabling of antitachycardia pacing functions.

DISCUSSION

This report describes the safety and efficacy of an implanted device that combines antitachycardia pacing with defibrillator functions and focuses on the use of telemetered information including events logged in memory. At follow-up, the device was used in 11 of 20 patients, and 5 died or had the device removed (2 for witnessed nonsudden deaths and 3 for heart transplant) (Table I). With 1 exception, these 5 patients all had extensive use of both antitachycardia pacing and shock delivery functions, and illustrate the use of these devices in selected patients awaiting cardiac transplantation.[3]

Lead system malfunction occurred in 3 of 20 patients. In all cases, the diagnosis of a lead system malfunction was obtained by comparison of the stored logic-circuitry signal output with the endocardial signal from either stored or real-time events. In the example shown (Figure 3), on-line telemetry supported the diagnosis by demonstrating nonphysiologic RR intervals during presumed make-break potentials. These may not always be present, in which case the ability of the device to store the logic-circuitry signal for later analysis is helpful in obtaining the correct diagnosis and is an improvement over clinical inference from analysis of RR intervals from display of the analog endocardial signal.[4]

Analysis of the RR intervals enabled assignment of the propriety of device therapy when it corresponded to the logic-circuitry output. With the aid of the device's internal 24-hour clock, the rhythm diagnosis can also be correlated with symptoms. In 1 case (Table II), the patient received appropriate device therapy despite the absence of symptoms. By prior classification systems, this could have been misclassified as inappropriate shock therapy.[5] There were no episodes of nonsustained tachycardia leading to shock, further underscoring the use of a noncommitted device.

Tachycardia detection and delivery of therapy depend on the sensing of the ventricular endocardial signal with therapy delivered according to a detected rate. This method of tachycardia detection cannot exclude a supraventricular tachycardia and was responsible for reprogramming the tachycardia detection rate in 2 patients. In the future, analysis of the frequency content[6] or some other aspect of the endocardial signal may enable proper assignment of the origin of a stored signal. Future sensors may incorporate variables related to hemodynamic tolerance in addition to those related to rate,[7,8] or perhaps separate implanted monitors to enable storage of the surface electrocardiogram.[9]

It would seem appropriate to consider use of these newer devices in all cases where an implantable cardioverter defibrillator would be used. Their advantages over noninvestigational devices are based on their antitachycardia and bradycardia pacing capabilities, enhanced telemetry and memory, as well as their automatic capacitor reformation capabilities that will decrease the frequency of visits needed. The telemetry and memory capabilities in particular obviate the need for more cumbersome patient- or device-activated monitors to assess the circumstances surrounding a shock.[10] Furthermore, these capabilities enable the rapid identification of lead fracture, ineffective or accelerating antitachycardia pacing, or frequent episodes of asymptomatic arrhythmias. This may decrease the time and costs that are often associated with the assessment of shock therapy.

These newer systems may also allow for controlled studies of drug therapy or provide further insights into the mechanisms of recurrent lethal arrhythmias, other than that available from fortuitous Holter recordings in selected patients.[11,12] Furthermore, these systems may enable a better understanding of the relation of induced arrhythmias and their termination to actual clinical events. For example, pace acceleration of ventricular tachycardia may be a statistical phenomenon, because it

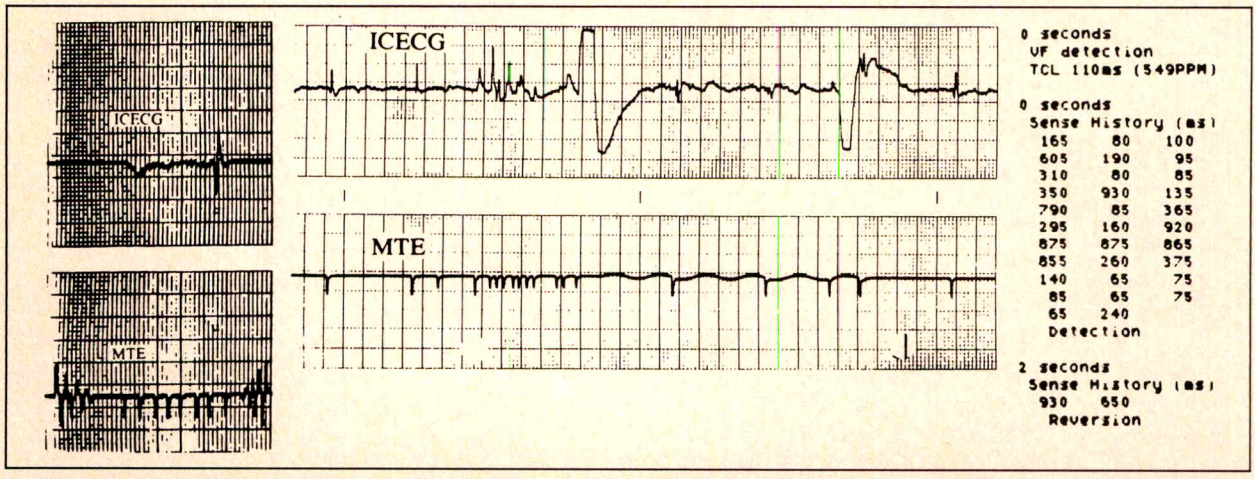


FIGURE 3. Intracardiac and logic-circuit telemetry from patient with fractured lead. *Left,* stored telemetry at time of shock delivery. Timing event marker records 8 events, while simultaneous intracardiac electrogram (ICECG) notes 1 beat. Paper speed is 25 mm/s. *Middle,* on-line telemetry at clinic follow-up. Intracardiac and timing event signals are recorded during mechanical movement of pulse generator. This reveals frequent detections on timing event channel, with onset of wavy line indicating onset of sensed event. Simultaneous intracardiac signal displays normal rhythm. Paper speed is 25 mm/s. *Right,* sense history of RR intervals leading to detection for episode displayed in *middle panels above.* Frequent nonphysiologic RR intervals are seen. MTE = main timing event; TCL = tachycardia cycle length; VF = ventricular fibrillation.

was not seen in the 13 of 20 patients with repeated ventricular tachycardia induction at the electrophysiologic study before discharge, but was observed in 5.3% of 874 spontaneous ventricular tachycardia episodes.

Acknowledgment: The assistance of Adriana Genga, RN, in patient care and follow-up, and the secretarial efforts of Fatima Moloo are gratefully acknowledged.

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Exercise Hyperventilation Chronic Congestive Heart Failure, and Its Relation to Functional Capacity and Hemodynamics

Marco Metra, MD, Livio Dei Cas, MD, Gaia Panina, MD, and Odoardo Visioli, MD

The ventilatory response to exercise was evaluated in 26 normal sedentary men and 68 patients with chronic heart failure using the slope of the relation between minute ventilation (VE) and carbon dioxide production (VCO_2). All subjects underwent maximal upright bicycle cardiopulmonary exercise testing; 33 patients also underwent right-sided cardiac catheterization. The slope of VE/VCO_2 was calculated by linear regression analysis using data from all the exercise tests and the first 60% of exercise duration; a high correlation was seen between these results ($r = 0.83$; $p < 0.001$). The slope of VE/VCO_2 was significantly, though weakly, related to peak exercise work load, oxygen consumption and ventilatory threshold ($r = -0.49$, -0.56 and -0.49, respectively), several peak exercise hemodynamic parameters and peak exercise dead space/tidal volume ratio ($r = 0.70$). With use of multivariate analysis, the only independent determinants of the slope were peak exercise dead space/tidal volume ratio and cardiac index. Thus, in patients with heart failure, exercise hyperventilation can contribute to the impairment of functional capacity and can be considered a compensatory response to abnormal hemodynamics and lung blood distribution in order to keep blood gas concentrations normal.

(Am J Cardiol 1992;70:622–628)

Peak oxygen consumption (VO_2) and ventilatory threshold are the 2 parameters most often used to quantitate exercise capacity in patients with chronic heart failure.[1–7] However, both parameters have important limits[8–11]; it is therefore necessary that exercise capacity be assessed also using other parameters independent of patient's motivation and which can be attained using submaximal effort. Minute ventilation (VE) during exercise is significantly increased in patients with heart failure compared with normal subjects.[3,12–18] To date, the ventilatory response to exercise has mainly been assessed using the minute VE to carbon dioxide production (VE/VCO_2) ratio at peak exercise.[16,17] Because VE is closely related to VCO_2,[3,13,15,18] an alternative way to assess VE/VCO_2 would be to evaluate the slope of the relation between minute VE and VCO_2[18,19]; this would not require performance of a maximal exercise test.

The aims of our study were to (1) verify the presence of a significant relation between minute VE and VCO_2 during exercise so that a value of slope of the VE/VCO_2 relation can be obtained; (2) assess whether this parameter can be calculated also using submaximal work loads; (3) determine whether it is significantly different between normal subjects and patients with heart failure and correlate it with the other measurements of functional capacity; and (4) determine its hemodynamic determinants.

METHODS

Patients: We studied 26 normal sedentary men and 68 male patients with chronic heart failure (Table I). Normal subjects underwent a preliminary rest and exercise electrocardiogram and spirometry; subjects aged >45 years also underwent rest-exercise thallium-201 myocardial scintigraphy. Patients whose pulmonary function test results were abnormal or whose exercise tests were suggestive of myocardial ischemia were excluded from the study.

All patients with heart failure were physically active outpatients and complained of dyspnea or fatigue, or both, during effort. They presented with a cardiothoracic ratio of >55% on the chest roentgenogram and a depressed left ventricular ejection fraction (<0.40; range 0.11 to 0.39) determined by radionuclide or contrast ventriculography. All patients had a documented history of pulmonary edema or fluid retention but had been clinically stable for ≥3 months before the study. Patients with a recent myocardial infarction (<4 months), angina pectoris, primary valvular heart disease, intermittent claudication or obstructive pulmonary disease, detected by lung function tests or blood gas

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This study was supported by the target project FATMA of the National Council of Research, Rome, Italy. Manuscript received January 16, 1992; revised manuscript received and accepted April 11, 1992.
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analysis, were excluded. Patients with symptoms or signs of myocardial ischemia during exercise testing, exercise-induced malignant ventricular arrhythmias, electronic pacemakers or evidence of sinus or atrioventricular node dysfunction were also excluded. All patients were taking digoxin and diuretic drugs (furosemide 20 to 250 mg/day plus spironolactone 100 mg in 36 patients); all drugs were administered ≥12 hours before the study. All vasodilators were withheld ≥72 hours before the study so that their administration did not interfere with the hemodynamic response to exercise.

Exercise testing: All patients underwent ≥2 preliminary exercise tests with expiratory gas monitoring 2 to 14 days before the study in order to familiarize themselves with this procedure. The variability of peak VO_2 and ventilatory threshold between the 2 last consecutive tests was ≤1.5 ml/kg/min in all cases.

Exercise tests were performed 3 to 4 hours after a light meal with the patient sitting upright on a bicycle ergometer. After a minimal rest period of 5 minutes, exercise was begun with 1 minute of unloaded pedaling (0 W) with work load increments of 20 W every 2 minutes in the patients and 20 W/min in the normal subjects; the velocity was 50 rpm until the appearance of limiting dyspnea or fatigue. The different work load increments of the normal subjects and the patients with heart failure was chosen in order to obtain an exercise duration ranging between 5 and 15 minutes, which has been shown to allow achievement of the highest values of peak VO_2.[20]

Heart rate and rhythm were continuously monitored by the electrocardiogram; blood pressure was measured by standard cuff sphygmomanometry. Patients with chest pain, serious cardiac arrhythmias or, in the presence of coronary artery disease, exercise-induced ST-segment depression ≥1 mm during the test, were excluded from the study. Expiratory gas monitoring was performed in all patients and normal subjects; 33 patients with heart failure also underwent simultaneous hemodynamic monitoring with right-sided cardiac catheterization. Cardiopulmonary exercise testing was repeated on 2 consecutive days at the same time of the day in 14 patients in order to assess reproducibility of the slope of VE/VCO_2.

Ventilatory parameters: Gas exchange analysis was performed with the patient breathing into a low resistance valve (Hans Rudolph model; dead space: 100 ml) with the nose clamped. Expired flow and oxygen and carbon dioxide partial pressures were continuously monitored on a breath-by-breath basis using a 2001 Medical Graphics System equipment.

TABLE I Clinical Features of the Study Group

	Normal Subjects	Patients with Heart Failure
No. of pts.	25	68
Age (mean) (years)	47 ± 12	51 ± 10
Diagnosis		
Idiopathic cardiomyopathy		42
Previous myocardial infarction		26
New York Heart Association functional class		
II		33
III		35
LVEF		
<20%		12
20–30%		35
>30%		21

LVEF = left ventricular ejection fraction.

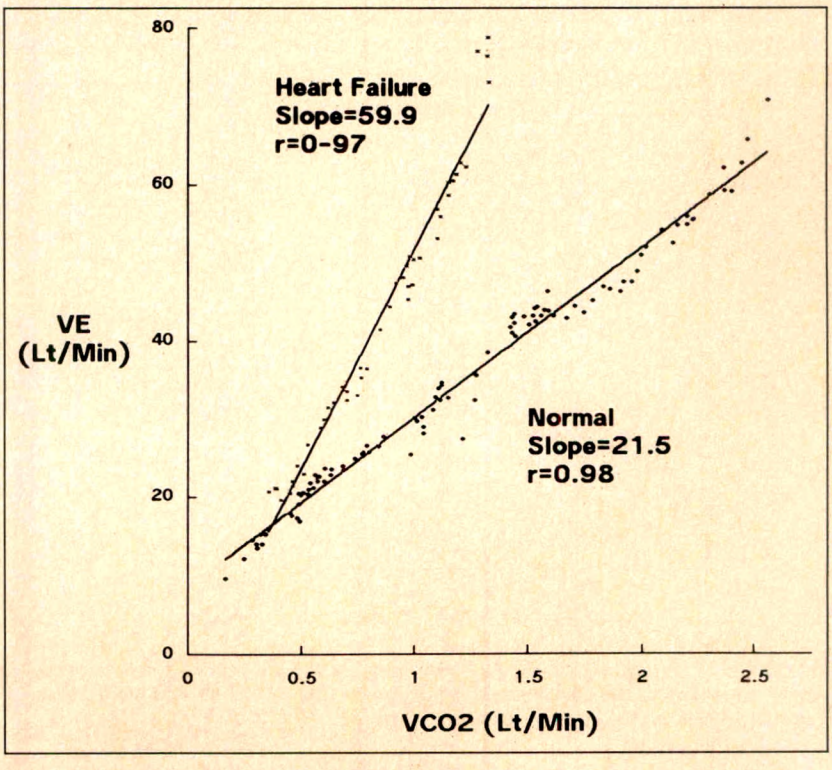


FIGURE 1. Examples of calculation of the slope of the relation between minute ventilation (VE) and carbon dioxide production (VCO2) in a normal subject and a patient with heart failure. Lt = liters.

Peak VO_2 was calculated averaging the values of the final 30 seconds of exercise. The ventilatory threshold was determined as the level of VO_2 at which an increase in the ventilatory equivalent of oxygen was observed without a simultaneous change in the ventilatory equivalent of carbon dioxide and an increase in end tidal oxygen tension without a simultaneous change in end tidal carbon dioxide tension.[3,6,21–23] Because we selected only trained patients with reproducible values of peak VO_2 and ventilatory threshold, we were able to determine the ventilatory threshold in 25 of 26 normal subjects and 67 of 68 of the studied patients.

The slope of the VE/VCO_2 relation was calculated by linear regression analysis using the values of minute VE and VCO_2 averaged every 10 seconds of exercise (Figure 1). To determine whether the slope remains constant throughout exercise and can be calculated after submaximal exercise, the data from each subject were reanalyzed using only the values obtained from the first 60 and 30% of exercise duration.

The dead space/tidal volume ratio was calculated in the 33 patients who also underwent the invasive study using the modified alveolar gas equation.[16,24,25]

Hemodynamic parameters: Thirty-three patients with chronic heart failure underwent radial artery cannulation and right-sided cardiac catheterization. Measured hemodynamic parameters included systolic and diastolic pulmonary artery, pulmonary capillary wedge and mean right atrial pressures. When diastolic pulmonary artery and pulmonary capillary wedge pressures differed ≤2 mm Hg, the former was used as an index of the wedge pressure itself. Cardiac output was determined by the Fick method. Blood samples for oxymetry were obtained during each stage of exercise from the distal lumen of the Swan-Ganz catheter and the arterial cannula. Derived hemodynamic parameters were calculated according to standard formulas.[26] Hemodynamic measurements and exercise testing were performed after a resting equilibration period of ≥4 hours after catheter's insertion.

Statistical analysis: All data are expressed as mean ± standard deviation. Differences between patients and normal subjects were assessed using unpaired *t* test. Relations between the slope VE/VCO_2 and the other parameters of functional capacity and hemodynamic measurements were assessed by linear regression analysis. Multivariate stepwise regression analysis was used to evaluate the independent predictive value of the parameters significantly related to the measurements of functional capacity by simple regression analysis. A p value <0.05 was considered statistically significant.

RESULTS

Exercise was primarily limited by fatigue in all patients and normal subjects; 42 patients also complained of dyspnea.

Minute VE was significantly related to VCO_2 in all normal subjects ($r = 0.98 \pm 0.01$; range 0.96 to 0.99; $p < 0.001$ in all cases) and patients with heart failure ($r = 0.97 \pm 0.03$; range 0.80 to 1; $p < 0.001$ in all cases) so that the slope of the relation between minute VE and VCO_2 could always be calculated. A significant relation was also present when data from only the first 60% of exercise duration were used ($r = 0.97 \pm 0.02$, range 0.86 to 0.99 in normal subjects; and $r = 0.95 \pm 0.04$, range 0.81 to 1 in patients with heart failure; $p < 0.001$ in all cases). Lower but still significant relations were obtained in normal subjects ($r = 0.91 \pm 0.11$; range 0.48 to 0.99) and patients ($r = 0.90 \pm 0.12$; range 0.31 to 1) using only the first 30% of exercise duration. The correlations between slopes obtained using the whole exercise test and only its first 60 and 30% are shown in Figure 2.

Exercise data are summarized in Table II. The slope of VE/VCO_2 was significantly higher in the patients than in the control group (36 ± 10 vs 28 ± 4; p

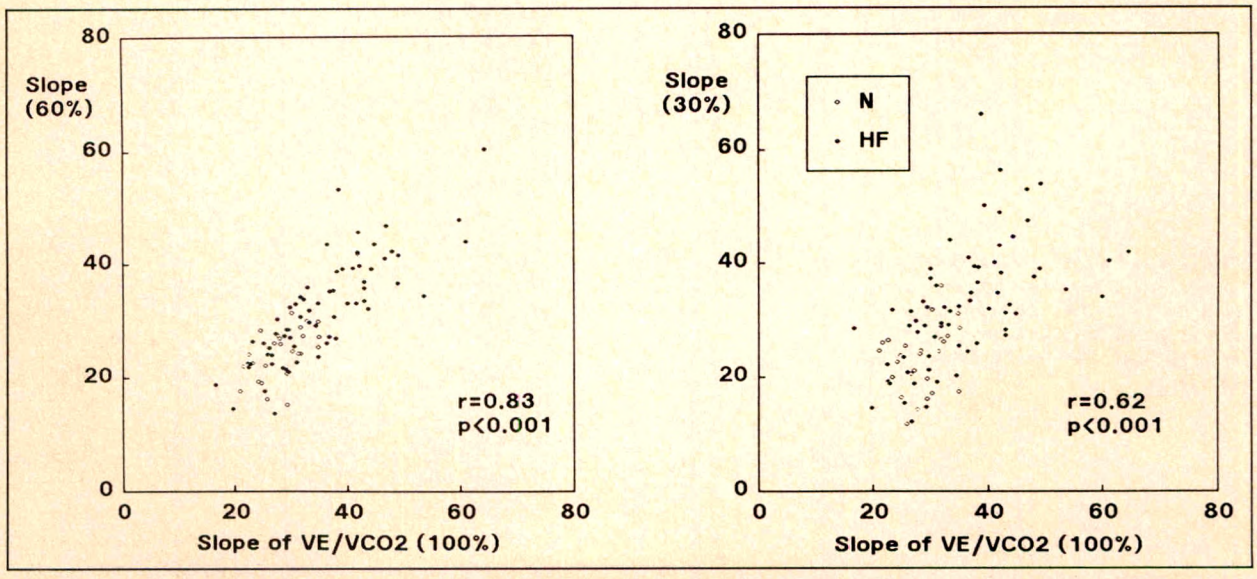


FIGURE 2. Correlations between the values of the slope of minute ventilation and carbon dioxide production (VE/VCO2) calculated using data of the whole exercise test (slope 100%), and its first 60% (slope 60%) and 30% (slope 30%). HF = patients with heart failure; N = normal subjects.

TABLE II Ergometric and Respiratory Parameters at Peak Exercise in Normal Subjects and Patients with Heart Failure

	Normal Subjects	Patients with Heart Failure
Work load (W)	163 ± 35	95 ± 45*
Oxygen consumption (ml/min)	2,327 ± 444	1,256 ± 505*
Oxygen consumption (ml/kg/min)	31 ± 7	17 ± 6*
Ventilatory threshold (ml/kg/min)	22 ± 5	12 ± 4*
Carbon dioxide production (ml/min)	2,501 ± 561	1,316 ± 529*
Respiratory exchange ratio (VCO_2/VO_2)	1.07 ± 0.13	1.07 ± 0.20
Minute ventilation (liters/min)	79 ± 16	50 ± 15*
Respiratory rate (breaths/min)	31 ± 6	31 ± 8
Tidal volume (ml/min)	2,536 ± 353	1,696 ± 458*
VE/VO_2	34 ± 6	43 ± 13†
VE/VCO_2	32 ± 4	40 ± 9*
Slope of VE/VCO_2	28 ± 4	36 ± 10*
Slope of VE/VCO_2 (60%)	24 ± 4	32 ± 9*
Slope of VE/VCO_2 (30%)	23 ± 6	33 ± 11*

Significance: *$p < 0.001$; †$p < 0.01$.
VE/VCO_2 = ventilatory equivalent of carbon dioxide production; VE/VO_2 = ventilatory equivalent of oxygen consumption; Slope of VE/VCO_2 (60%) = slope of VE/VCO_2 relation using data from the first 60% of exercise; Slope of VE/VCO_2 (30%) = slope of VE/VCO_2 relation using data from the first 30% of exercise.

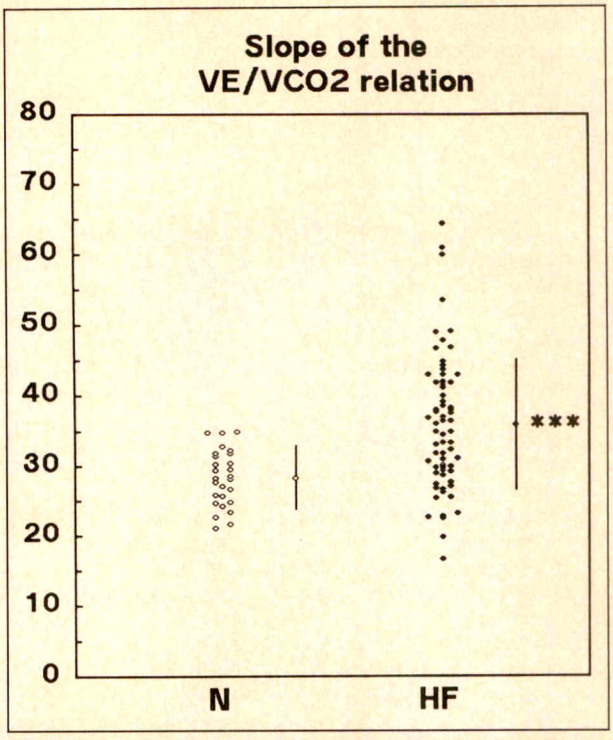


FIGURE 3. Individual values of the slope of minute ventilation and carbon dioxide production (VE/VCO2) in normal subjects (N) and in patients with heart failure (HF). ***p <0.001 between normal subjects and patients with heart failure.

<0.001). With regard to individual values, no normal subject had a value of slope ≥35, whereas a wide distribution of values was seen in patients with heart failure (Figure 3). This distribution was related to the variability of functional capacity of the patients with heart failure. In fact, a significant, though rather weak, inverse correlation between the slope VE/VCO_2 and peak exercise work load, peak VO_2 and ventilatory threshold was found in the entire study group ($r = -0.49$, -0.56 and -0.49; $p < 0.001$ in all cases) (Figure 4) and in patients with heart failure, considered separately ($r = -0.42$, -0.56 and -0.42; $p < 0.001$ in all cases). In contrast, normal subjects did not have a significant correlation with peak exercise workload, VO_2 and ventilatory threshold ($r = 0.12$, -0.07 and -0.22, respectively). Reproducibility of the slope VE/VCO_2 is shown in Figure 5.

Hemodynamic data at rest and peak exercise of the 33 patients who underwent right-sided cardiac catheterization are summarized in Table III. No patient presented >5% arterial oxygen desaturation or >6 mm Hg arterial partial pressure of carbon dioxide increase over resting values at peak exercise. Relations between the slope VE/VCO_2 and resting and exercise hemodynamics are listed in Table IV and Figure 6. With use of multiple stepwise regression analysis, only the dead space/tidal volume ratio and cardiac index were independently related to the VE/VCO_2 slope (F to enter = 29.33 and 13.27, respectively). Similar relations, except for a weaker correlation with dead space/tidal volume ratio, were found between the 2 other measures of functional capacity, peak VO_2 and ventilatory threshold, and rest and exercise hemodynamics (Table IV). Using

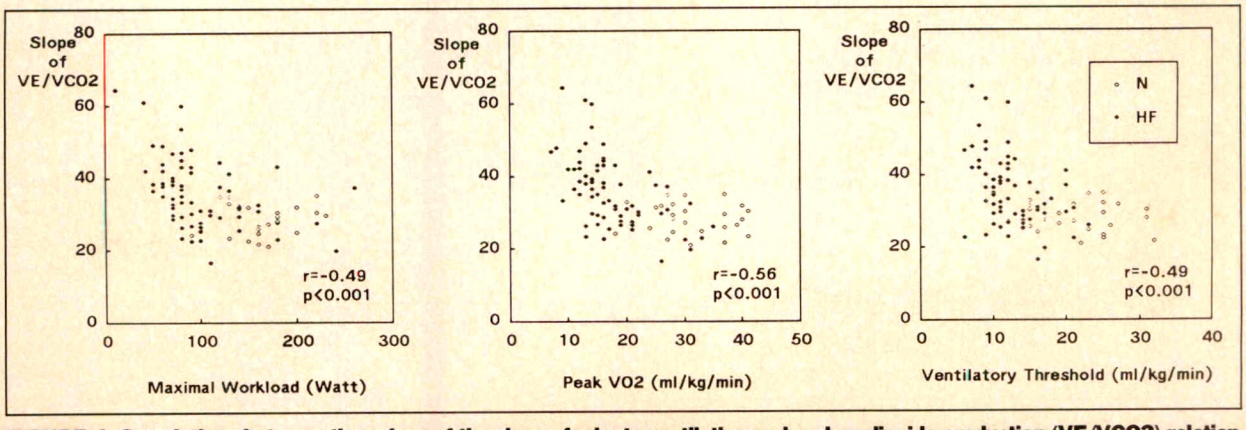


FIGURE 4. Correlations between the values of the slope of minute ventilation and carbon dioxide production (VE/VCO2) relation and peak exercise work load, oxygen consumption (V02) and ventilatory threshold, expressed as the corresponding value of oxygen consumption. Other abbreviations as in Figure 2.

TABLE III Hemodynamic Parameters at Rest and Peak Exercise in Patients with Heart Failure (n = 33)

	Rest	Peak Exercise
Heart rate (beats/min)	86 ± 19	147 ± 24
Mean arterial pressure (mm Hg)	91 ± 9	110 ± 19
Cardiac index (liters/min/m^2)	2.33 ± 0.63	5.39 ± 2.26
Stroke volume index (ml/beat/m^2)	29 ± 10	37 ± 13
Stroke work index (g/beat/m^2)	29 ± 12	39 ± 26
Systemic vascular resistance (dynes s cm^{-5})	1,706 ± 469	896 ± 304
Oxygen extraction (%)	36 ± 8	70 ± 9
Right atrial pressure (mm Hg)	6 ± 3	12 ± 6
Mean pulmonary artery pressure (mm Hg)	25 ± 12	48 ± 14
Pulmonary wedge pressure (mm Hg)	17 ± 10	38 ± 12
Total pulmonary resistance (dynes s cm^{-5})	493 ± 272	482 ± 264
Pulmonary vascular resistance (dynes s cm^{-5})	140 ± 73	102 ± 63
Oxygen arterial saturation (%)	98 ± 3	97 ± 3
Carbon dioxide arterial partial pressure (mm Hg)	41 ± 2	38 ± 4
Oxygen consumption (ml/kg/min)	3 ± 1	17 ± 6
Dead space/tidal volume ratio	0.54 ± 0.12	0.29 ± 0.06

multivariate stepwise regression analysis, peak VO_2 was related only to peak exercise cardiac index and total pulmonary resistance (F to enter = 120.58 and 4.46, respectively) and, similarly, ventilatory threshold was related only to peak exercise cardiac index (F to enter = 56.46); dead space/tidal volume ratio was never selected as an independent variable related to these last 2 measurements.

DISCUSSION

In our study, we demonstrated the feasibility of assessing the exercise ventilatory response using the slope of the relation between minute VE and VCO_2. Because the slope does not change throughout exercise, this parameter can be calculated using the data of both the whole exercise test and its first 60%. Therefore, it is an objective measurement that can be calculated also using submaximal exercise tests.

The slope of VE/VCO_2 was significantly different between patients with heart failure and normal subjects; it was steeper in patients with reduced functional capacity. This parameter was significantly related to peak VO_2 with a correlation coefficient ($r = -0.56$; $p < 0.001$) similar to the one obtained by Fink et al[15] using a value of minute VE extrapolated at a VCO_2 of 1 liter/min ($r = -0.59$); however, this correlation is lower than the one reported on in the only previous study in which the slope of VE/VCO_2 was related to peak VO_2 ($r = -0.86$).[19] This discrepancy may depend on differences in the study groups or on the use of bicycle rather than treadmill exercise testing in our and Fink's study.

The rather weak correlation between the slope VE/VCO_2 and peak VO_2 and ventilatory threshold shows that these parameters are determined by different factors. In fact, the dead space/tidal volume ratio was an independent determinant of the slope VE/VCO_2 but was not related to peak VO_2 and ventilatory threshold by multivariate analysis. The weak correlation between VE/VCO_2 and peak VO_2 shows that the first parameter cannot be used to predict maximal exercise performance in an individual patient. The clinical interest in the VE/VCO_2 slope stems from the possibility of calcu-

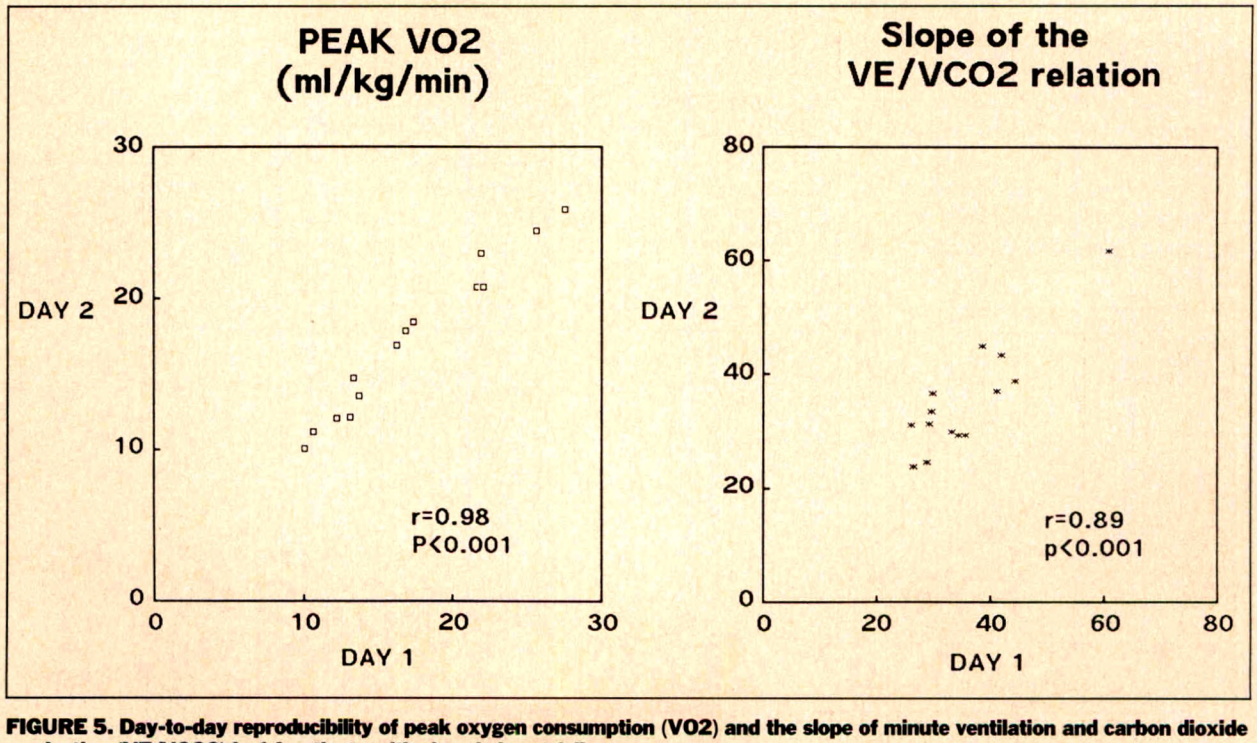


FIGURE 5. Day-to-day reproducibility of peak oxygen consumption (VO2) and the slope of minute ventilation and carbon dioxide production (VE/VCO2) in 14 patients with chronic heart failure.

lating it by also using submaximal exercises and from its independence of patient's motivation; however, its clinical value must be assessed in further studies evaluating its prognostic value and its sensitivity to changes induced by therapy.

Our study confirms previous reports showing that minute VE is closely coupled to VCO_2 in patients with heart failure.[13,15,16] The increased ventilatory response to exercise of patients with heart failure can thus be considered a compensatory response to their increased pulmonary dead space and abnormal hemodynamics in order to keep arterial blood gas tension within normal limits even during maximal exercise. The correlation between the slope VE/VCO_2 and peak VO_2 in such pa-

TABLE IV Single Correlations Between Hemodynamic and Respiratory Parameters at Rest and Peak Exercise in Patients with Heart Failure (n = 33)

	Slope VE/VCO_2		Peak VO_2		Ventilatory Threshold	
	Rest	Ex.	Rest	Ex.	Rest	Ex.
Heart rate (beats/min)	−0.04	−0.41‡	−0.15	0.45†	−0.08	0.45†
Mean arterial pressure (mm Hg)	−0.11	−0.31	0.08	0.63*	−0.05	0.60*
Cardiac index (liters/min/m^2)	−0.19	−0.69*	0.25	0.89*	0.33	0.80*
Stroke volume index (ml/beat/m^2)	−0.12	−0.62*	0.19	0.76*	0.20	0.68*
Stroke work index (g/beat/m^2)	−0.28	−0.55*	0.36‡	0.77*	0.35‡	0.71*
Systemic vascular resistance (dynes s cm^{-5})	0.21	0.63*	−0.26	−0.63*	−0.38‡	−0.54*
Oxygen extraction (%)	0.23	0.33	−0.24	0.08	−0.29	0.08
Right atrial pressure (mm Hg)	0.17	0.38‡	−0.26	−0.40‡	−0.33	−0.42‡
Mean pulmonary artery pressure (mm Hg)	−0.36‡	0.43‡	−0.35‡	−0.33	−0.37‡	−0.40‡
Pulmonary wedge pressure (mm Hg)	0.37‡	0.48†	−0.36‡	−0.38‡	−0.37‡	−0.41‡
Total pulmonary resistance (dynes s cm^{-5})	0.44†	0.68*	−0.41‡	−0.64*	−0.46†	−0.62*
Pulmonary vascular resistance (dynes s cm^{-5})	0.28	0.29	−0.25	−0.25	−0.31	−0.37‡
Dead space/tidal volume ratio	0.10	0.70*	0.10	−0.42‡	−0.13	−0.35‡

‡p < 0.05.
Ex. = exercise.
Explanation of other symbols and abbreviations as in Table II.

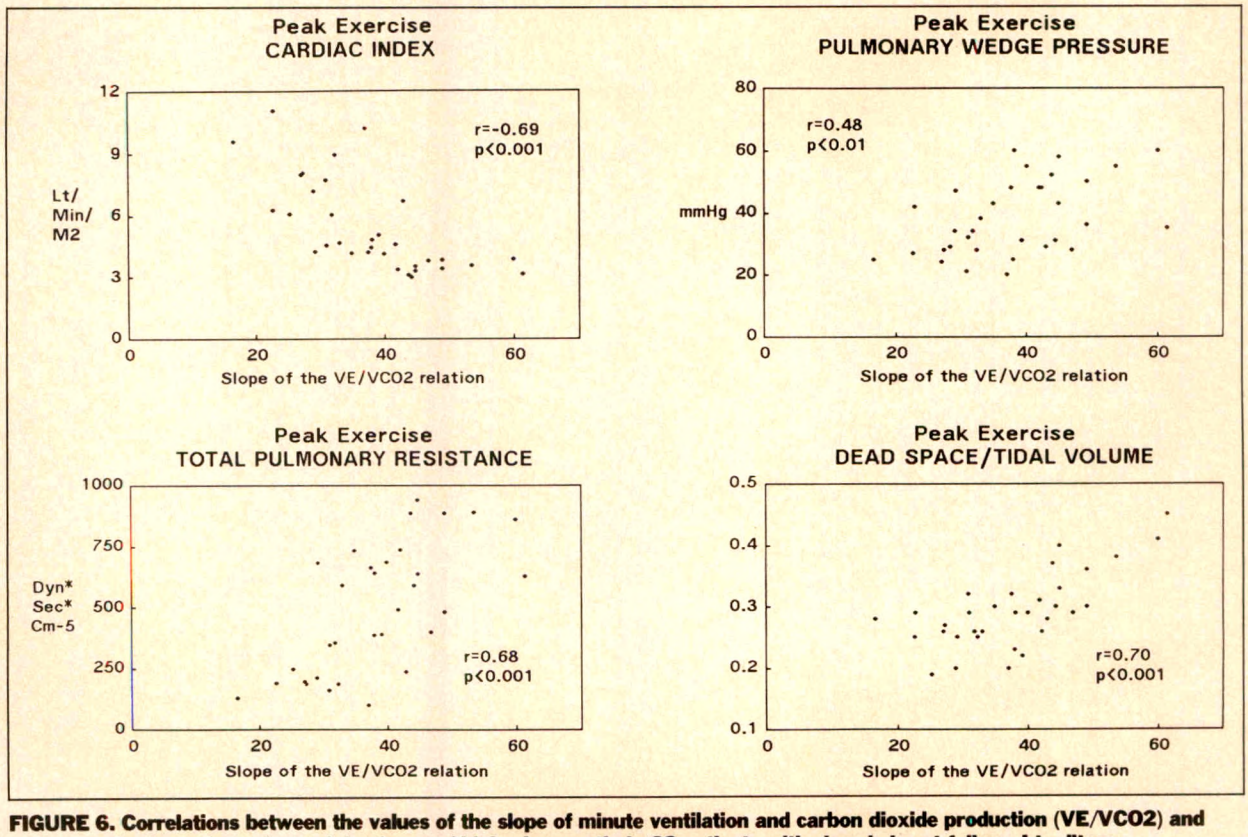


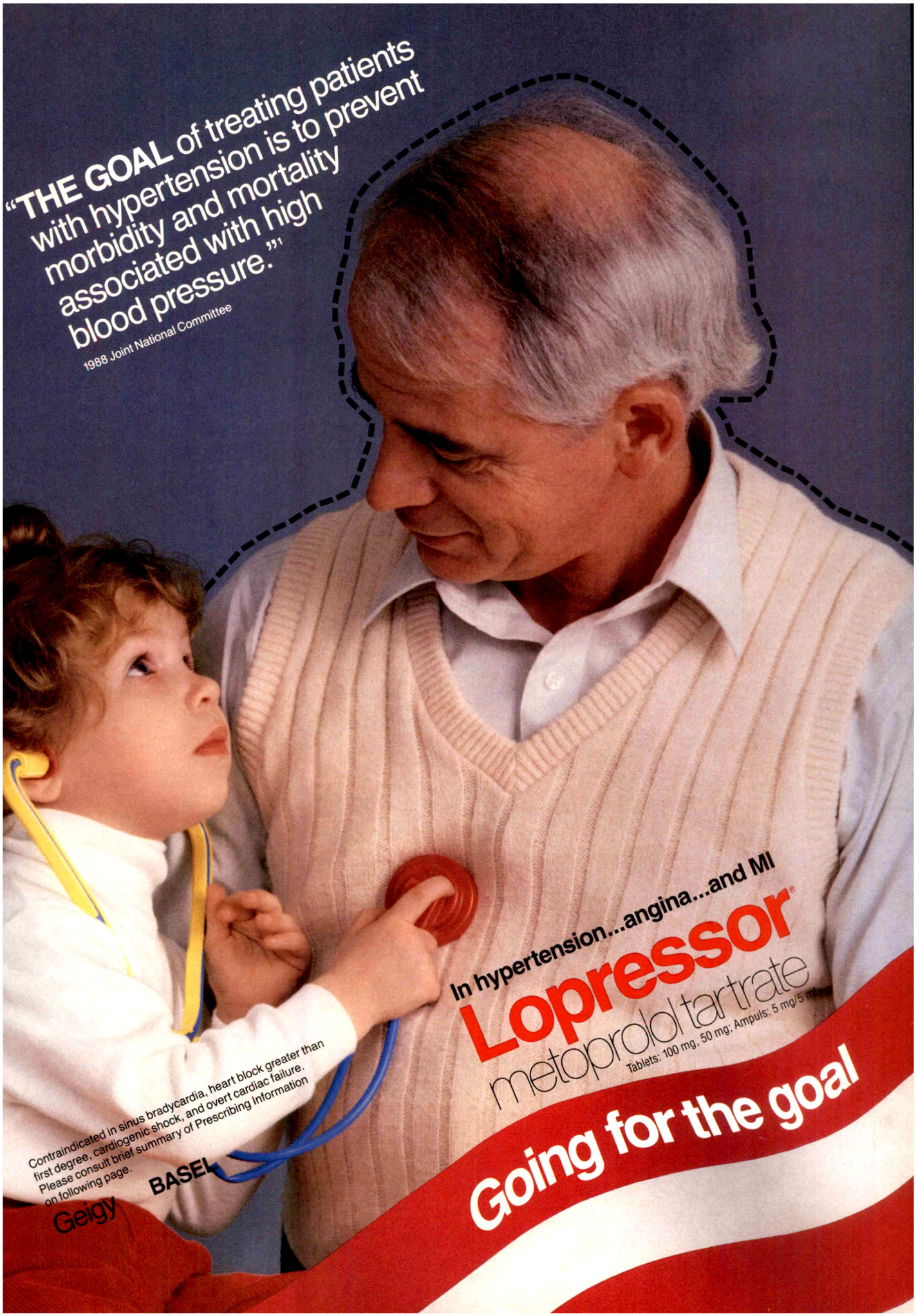
FIGURE 6. Correlations between the values of the slope of minute ventilation and carbon dioxide production (VE/VCO2) and peak exercise hemodynamics and dead space/tidal volume ratio in 33 patients with chronic heart failure. Lt = liters.

tients but not in normal subjects shows that this mechanism may contribute to the impairment of functional capacity of patients with heart failure.

Acknowledgment: We thank Chiara Pioselli for her help in the preparation of this manuscript.

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BRIEF SUMMARY (FOR FULL PRESCRIBING INFORMATION, SEE PACKAGE INSERT)

INDICATIONS AND USAGE

Hypertension
Lopressor tablets are indicated for the treatment of hypertension. They may be used alone or in combination with other antihypertensive agents.

Angina Pectoris
Lopressor is indicated in the long-term treatment of angina pectoris.

Myocardial Infarction
Lopressor ampuls and tablets are indicated in the treatment of hemodynamically stable patients with definite or suspected acute myocardial infarction to reduce cardiovascular mortality. Treatment with intravenous Lopressor can be initiated as soon as the patient's clinical condition allows (see **DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS,** and **WARNINGS**). Alternatively, treatment can begin within 3 to 10 days of the acute event (see **DOSAGE AND ADMINISTRATION**).

CONTRAINDICATIONS

Hypertension and Angina
Lopressor is contraindicated in sinus bradycardia, heart block greater than first degree, cardiogenic shock, and overt cardiac failure (see **WARNINGS**).

Myocardial Infarction
Lopressor is contraindicated in patients with a heart rate < 45 beats/min; second- and third-degree heart block; significant first-degree heart block (P-R interval ≥ 0.24 sec); systolic blood pressure < 100 mmHg; or moderate-to-severe cardiac failure (see **WARNINGS**).

WARNINGS

Hypertension and Angina
Cardiac Failure: Sympathetic stimulation is a vital component supporting circulatory function in congestive heart failure, and beta blockade carries the potential hazard of further depressing myocardial contractility and precipitating more severe failure. In hypertensive and angina patients who have congestive heart failure controlled by digitalis and diuretics, Lopressor should be administered cautiously. Both digitalis and Lopressor slow AV conduction.
In Patients Without a History of Cardiac Failure: Continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or given a diuretic. The response should be observed closely. If cardiac failure continues, despite adequate digitalization and diuretic therapy, Lopressor should be withdrawn.

Ischemic Heart Disease: Following abrupt cessation of therapy with certain beta-blocking agents, exacerbations of angina pectoris and, in some cases, myocardial infarction have occurred. When discontinuing chronically administered Lopressor, particularly in patients with ischemic heart disease, the dosage should be gradually reduced over a period of 1-2 weeks and the patient should be carefully monitored. If angina markedly worsens or acute coronary insufficiency develops, Lopressor administration should be reinstated promptly, at least temporarily, and other measures appropriate for the management of unstable angina should be taken. Patients should be warned against interruption or discontinuation of therapy without the physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue Lopressor therapy abruptly even in patients treated only for hypertension.

Bronchospastic Diseases: **PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD, IN GENERAL, NOT RECEIVE BETA BLOCKERS. Because of its relative beta$_1$ selectivity, however, Lopressor may be used with caution in patients with bronchospastic disease who do not respond to, or cannot tolerate, other antihypertensive treatment. Since beta$_1$ selectivity is not absolute, a beta$_2$-stimulating agent should be administered concomitantly, and the lowest possible dose of Lopressor should be used. In these circumstances it would be prudent initially to administer Lopressor in smaller doses three times daily, instead of larger doses two times daily, to avoid the higher plasma levels associated with the longer dosing interval. (See DOSAGE AND ADMINISTRATION.)**
Major Surgery: The necessity or desirability of withdrawing beta-blocking therapy prior to major surgery is controversial; the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures.

Lopressor, like other beta blockers, is a competitive inhibitor of beta-receptor agonists, and its effects can be reversed by administration of such agents, e.g., dobutamine or isoproterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in restarting and maintaining the heartbeat has also been reported with beta blockers.
Diabetes and Hypoglycemia: Lopressor should be used with caution in diabetic patients if a beta-blocking agent is required. Beta blockers may mask tachycardia occurring with hypoglycemia, but other manifestations such as dizziness and sweating may not be significantly affected.
Thyrotoxicosis: Beta-adrenergic blockade may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. Patients suspected of developing thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of beta blockade, which might precipitate a thyroid storm.

Myocardial Infarction
Cardiac Failure: Sympathetic stimulation is a vital component supporting circulatory function, and beta blockade carries the potential hazard of depressing myocardial contractility and precipitating or exacerbating minimal cardiac failure.

During treatment with Lopressor, the hemodynamic status of the patient should be carefully monitored. If heart failure occurs or persists despite appropriate treatment, Lopressor should be discontinued.
Bradycardia: Lopressor produces a decrease in sinus heart rate in most patients; this decrease is greatest among patients with high initial heart rates and least among patients with low initial heart rates. Acute myocardial infarction (particularly inferior infarction) may in itself produce significant lowering of the sinus rate. If the sinus rate decreases to < 40 beats/min, particularly if associated with evidence of lowered cardiac output, atropine (0.25-0.5 mg) should be administered intravenously. If treatment with atropine is not successful, Lopressor should be discontinued, and cautious administration of isoproterenol or installation of a cardiac pacemaker should be considered.
AV Block: Lopressor slows AV conduction and may produce significant first- (P-R interval ≥ 0.26 sec), second-, or third-degree heart block. Acute myocardial infarction also produces heart block.

If heart block occurs, Lopressor should be discontinued and atropine (0.25-0.5 mg) should be administered intravenously. If treatment with atropine is not successful, cautious administration of isoproterenol or installation of a cardiac pacemaker should be considered.
Hypotension: If hypotension (systolic blood pressure ≤ 90 mmHg) occurs, Lopressor should be discontinued, and the hemodynamic status of the patient and the extent of myocardial damage carefully assessed. Invasive monitoring of central venous, pulmonary capillary wedge, and arterial pressures may be required. Appropriate therapy with fluids, positive inotropic agents, balloon counterpulsation, or other treatment modalities should be instituted. If hypotension is associated with sinus bradycardia or AV block, treatment should be directed at reversing these (see above).
Bronchospastic Diseases: **PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD, IN GENERAL, NOT RECEIVE BETA BLOCKERS. Because of its relative beta$_1$ selectivity, Lopressor may be used with extreme caution in patients with bronchospastic disease. Because it is unknown to what extent beta$_2$-stimulating agents may exacerbate myocardial ischemia and the extent of infarction, these agents should *not* be used prophylactically. If bronchospasm not related to congestive heart failure occurs, Lopressor should be discontinued. A theophylline derivative or a beta$_2$ agonist may be administered cautiously, depending on the clinical condition of the patient. Both theophylline derivatives and beta$_2$ agonists may produce serious cardiac arrhythmias.**

PRECAUTIONS

General
Lopressor should be used with caution in patients with impaired hepatic function.

Information for Patients
Patients should be advised to take Lopressor regularly and continuously, as directed, with or immediately following meals. If a dose should be missed, the patient should take only the next scheduled dose (without doubling it). Patients should not discontinue Lopressor without consulting the physician.

Patients should be advised (1) to avoid operating automobiles and machinery or engaging in other tasks requiring alertness until the patient's response to therapy with Lopressor has been determined; (2) to contact the physician if any difficulty in breathing occurs; (3) to inform the physician or dentist before any type of surgery that he or she is taking Lopressor.

Laboratory Tests
Clinical laboratory findings may include elevated levels of serum transaminase, alkaline phosphatase, and lactate dehydrogenase.

Drug Interactions
Catecholamine-depleting drugs (e.g., reserpine) may have an additive effect when given with beta-blocking agents. Patients treated with Lopressor plus a catecholamine depletor should therefore be closely observed for evidence of hypotension or marked bradycardia, which may produce vertigo, syncope, or postural hypotension.
Risk of Anaphylactic Reaction: While taking beta-blockers, patients with a history of severe anaphylactic reaction to a variety of allergens may be more reactive to repeated challenge, either accidental, diagnostic, or therapeutic. Such patients may be unresponsive to the usual doses of epinephrine used to treat allergic reaction.

Carcinogenesis, Mutagenesis, Impairment of Fertility
Long-term studies in animals have been conducted to evaluate carcinogenic potential. In a 2-year study in rats at three oral dosage levels of up to 800 mg/kg per day, there was no increase in the development of spontaneously occurring benign or malignant neoplasms of any type. The only histologic changes that appeared to be drug related were an increased incidence of generally mild focal accumulation of foamy macrophages in pulmonary alveoli and a slight increase in biliary hyperplasia. In a 21-month study in Swiss albino mice at three oral dosage levels of up to 750 mg/kg per day, benign lung tumors (small adenomas) occurred more frequently in female mice receiving the highest dose than in untreated control animals. There was no increase in malignant or total (benign plus malignant) lung tumors, nor in the overall incidence of tumors or malignant tumors. This 21-month study was repeated in CD-1 mice, and no statistically or biologically significant differences were observed between treated and control mice of either sex for any type of tumor.

All mutagenicity tests performed (a dominant lethal study in mice, chromosome studies in somatic cells, a Salmonella/mammalian-microsome mutagenicity test, and a nucleus anomaly test in somatic interphase nuclei) were negative.

No evidence of impaired fertility due to Lopressor was observed in a study performed in rats at doses up to 55.5 times the maximum daily human dose of 450 mg.

Pregnancy Category C
Lopressor has been shown to increase postimplantation loss and decrease neonatal survival in rats at doses up to 55.5 times the maximum daily human dose of 450 mg. Distribution studies in mice confirm exposure of the fetus when Lopressor is administered to the pregnant animal. These studies have revealed no evidence of impaired fertility or teratogenicity. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers
Lopressor is excreted in breast milk in very small quantity. An infant consuming 1 liter of breast milk daily would receive a dose of less than 1 mg of the drug. Caution should be exercised when Lopressor is administered to a nursing woman.

Pediatric Use
Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Hypertension and Angina
Most adverse effects have been mild and transient.
Central Nervous System: Tiredness and dizziness have occurred in about 10 of 100 patients. Depression has been reported in about 5 of 100 patients. Mental confusion and short-term memory loss have been reported. Headache, nightmares, and insomnia have also been reported.
Cardiovascular: Shortness of breath and bradycardia have occurred in approximately 3 of 100 patients. Cold extremities; arterial insufficiency, usually of the Raynaud type; palpitations; congestive heart failure; peripheral edema; and hypotension have been reported in about 1 of 100 patients. (See **CONTRAINDICATIONS, WARNINGS,** and **PRECAUTIONS.**)
Respiratory: Wheezing (bronchospasm) and dyspnea have been reported in about 1 of 100 patients (see **WARNINGS**).
Gastrointestinal: Diarrhea has occurred in about 5 of 100 patients. Nausea, dry mouth, gastric pain, constipation, flatulence, and heartburn have been reported in about 1 of 100 patients.
Hypersensitive Reactions: Pruritus or rash have occurred in about 5 of 100 patients. Worsening of psoriasis has also been reported.
Miscellaneous: Peyronie's disease has been reported in fewer than 1 of 100,000 patients. Musculoskeletal pain, blurred vision, and tinnitus have also been reported.

There have been rare reports of reversible alopecia, agranulocytosis, and dry eyes. Discontinuation of the drug should be considered if any such reaction is not otherwise explicable.

The oculomucocutaneous syndrome associated with the beta blocker practolol has not been reported with Lopressor.

Myocardial Infarction
Central Nervous System: Tiredness has been reported in about 1 of 100 patients. Vertigo, sleep disturbances, hallucinations, headache, dizziness, visual disturbances, confusion, and reduced libido have also been reported, but a drug relationship is not clear.
Cardiovascular: In the randomized comparison of Lopressor and placebo described in the CLINICAL PHARMACOLOGY section, the following adverse reactions were reported:

	Lopressor	*Placebo*
Hypotension (systolic BP < 90 mmHg)	27.4%	23.2%
Bradycardia (heart rate < 40 beats/min)	15.9%	6.7%
Second- or third-degree heart block	4.7%	4.7%
First-degree heart block (P-R ≥ 0.26 sec)	5.3%	1.9%
Heart failure	27.5%	29.6%

Respiratory: Dyspnea of pulmonary origin has been reported in fewer than 1 of 100 patients.
Gastrointestinal: Nausea and abdominal pain have been reported in fewer than 1 of 100 patients.
Dermatologic: Rash and worsened psoriasis have been reported, but a drug relationship is not clear.
Miscellaneous: Unstable diabetes and claudication have been reported, but a drug relationship is not clear.

Potential Adverse Reactions
A variety of adverse reactions not listed above have been reported with other beta-adrenergic blocking agents and should be considered potential adverse reactions to Lopressor.
Central Nervous System: Reversible mental depression progressing to catatonia; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.
Cardiovascular: Intensification of AV block (see **CONTRAINDICATIONS**).
Hematologic: Agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.
Hypersensitive Reactions: Fever combined with aching and sore throat, laryngospasm, and respiratory distress.

OVERDOSAGE

Acute Toxicity
Several cases of overdosage have been reported, some leading to death.

Oral LD_{50}s (mg/kg): mice, 1158-2460; rats, 3090-4670.

Signs and Symptoms
Potential signs and symptoms associated with overdosage with Lopressor are bradycardia, hypotension, bronchospasm, and cardiac failure.

Treatment
There is no specific antidote.

In general, patients with acute or recent myocardial infarction may be more hemodynamically unstable than other patients and should be treated accordingly (see **WARNINGS, Myocardial Infarction**).

On the basis of the pharmacologic actions of Lopressor, the following general measures should be employed:
Elimination of the Drug: Gastric lavage should be performed.
Bradycardia: Atropine should be administered. If there is no response to vagal blockade, isoproterenol should be administered cautiously.
Hypotension: A vasopressor should be administered, e.g., levarterenol or dopamine.
Bronchospasm: A beta$_2$-stimulating agent and/or a theophylline derivative should be administered.
Cardiac Failure: A digitalis glycoside and diuretic should be administered. In shock resulting from inadequate cardiac contractility, administration of dobutamine, isoproterenol, or glucagon may be considered.

Geigy
C92-26 (Rev. 4/92)
GEIGY Pharmaceuticals
Division of CIBA-GEIGY Corporation
Ardsley, New York 10502

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Printed in USA (7/92) 536-22888-A 2

Effects of Acute and Chronic Ibopamine Administration on Resting and Exercise Hemodynamics, Plasma Catecholamines and Functional Capacity of Patients with Chronic Congestive Heart Failure

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The effects of acute and chronic ibopamine treatment on resting and exercise hemodynamics, exercise capacity and plasma catecholamines were evaluated in 25 patients with chronic heart failure, using a double-blind, parallel, placebo-controlled design.

During 2 months of therapy with either placebo or ibopamine (100 mg, 3 times daily), 1 patient was withdrawn from each group for worsening heart failure, New York Heart Association functional class improved in 4 patients on ibopamine and in 1 on placebo, and furosemide dose could be decreased in 4 on ibopamine and in no patient on placebo. Acute ibopamine administration induced, in comparison with placebo, a significant increase of cardiac and stroke volume indexes both at rest and peak exercise, with a reduction of systemic vascular resistance. These hemodynamic changes were maintained also after chronic therapy, with no evidence of tolerance development. Exercise capacity (evaluated as peak exercise duration and oxygen consumption, and ventilatory threshold) did not significantly change. Resting and peak exercise norepinephrine plasma levels were significantly reduced after both acute and chronic ibopamine administration. Thus, the hemodynamic and neurohumoral effects of ibopamine make this drug potentially useful for the chronic treatment of congestive heart failure.

(Am J Cardiol 1992;70:629–634)

Dopamine is known to exert beneficial hemodynamic and neurohumoral effects on patients with heart failure.[1–4] Ibopamine is 1 of the few dopamine derivatives available for oral administration; it is endogenously converted to N-methyldopamine, which is active on dopaminergic, β-2 and, to a lesser extent, β-1 and α-adrenergic receptors.[3,5,6] Many studies evaluating the effects of acute ibopamine administration have shown that it can significantly improve the hemodynamics of patients with heart failure.[7–10] However, the chronic efficacy of ibopamine remains controversial. Long-term therapy was associated with an attenuation of its effects in 1 study,[10] but not in another[11]; however, both these studies were not controlled with placebo. More recently, double-blind trials showed a persistent improvement of hemodynamics and exercise capacity after long-term therapy[12–14]; however, these studies were performed using only noninvasive methods that are less reproducible and accurate than right heart catheterization for the evaluation of drug therapy in patients with dilated cardiomyopathy.[15–17]

The aim of this study was to assess (using a randomized, double-blind, placebo-controlled design) the acute and chronic effects of ibopamine on rest and exercise hemodynamics, exercise capacity and plasma catecholamines in patients with chronic heart failure.

METHODS

Patients: The study group comprised 25 patients (20 men and 5 women; mean age 54 ± 13 years) with chronic congestive heart failure clinically stable for ≥3 months before entry in the study. No patient had angina or clinical or electrocardiographic signs of acute myocardial ischemia in the 3 months before the study. All patients had left ventricular dysfunction (left ventricular ejection fraction <0.35) and mild to moderate impairment of exercise capacity (peak oxygen consumption <25 ml/kg/min), and were receiving digoxin, diuretics (furosemide [25 to 250 mg], plus spironolactone [100 mg] in 8) and converting enzyme inhibitors (captopril [12.5 mg 3 times daily in 8, and 25 mg 3 times daily in 12], and enalapril [20 mg in 5]); 5 patients were also receiving isosorbide dinitrate (40 mg 3 times daily). Clinical features of the patients randomized to either placebo or ibopamine were not significantly different and are summarized in Table I. Each patient gave informed written consent before entry in the study.

Procedures: On the day before hemodynamic measurements and exercise testing, a triple-lumen Swan

From the Cattedra di Cardiologia, Universitá di Brescia, Brescia, Italy. This study was supported by the target project "FATMA" of the National Council of Research, Rome, Italy. Manuscript received January 16, 1992; revised manuscript received and accepted May 11, 1992.

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TABLE I Clinical Characteristics of the Two Treatment Groups

	Placebo	Ibopamine
No. of pts.	13	12
Age (year)	55 ± 12	57 ± 14
Sex (men)	10	10
Diagnosis		
Idiopathic dilated cardiomyopathy	7	8
Postinfarction dilated cardiomyopathy	6	4
New York Heart Association functional class		
II	5	4
III	8	8
Vasodilators		
Captopril	10	10
Enalapril	3	2
Nitrates	3	2

Ganz catheter was inserted percutaneously through an antecubital vein and positioned in the pulmonary artery. Measured hemodynamic variables included systolic and diastolic pulmonary artery pressures, pulmonary capillary wedge pressure and right atrial pressure. When diastolic pulmonary artery pressure and pulmonary wedge pressure differed ≤2 mm Hg, the former was used as an index of the wedge pressure itself. Cardiac output was determined using the Fick method. Systemic blood pressure was measured through an arterial cannula positioned in the radial artery. Derived hemodynamic parameters were calculated according to standard formulas.[18]

Gas exchange analysis was performed with the patient breathing into a low-resistance 2-way valve, with his nose clamped, using a 2001 Medical Graphics system. Exercise testing was performed with the patient in the sitting position, using an electronically braked cycle ergometer. Exercise was begun at a work load of 0 W with further increments of 20 W every 2 minutes, at the velocity of 50 rpm, up to the appearance of limiting dyspnea or fatigue. No patient had chest pain, serious cardiac arrhythmias or exercise-induced ST-segment depression ≥1 mm during the test. Electrocardiographic and respiratory parameters were continuously monitored; hemodynamic measurements were obtained at rest, after an equilibration period of ≥10 minutes, during the last minute of each work load increment and at maximal exercise.

Exercise capacity was evaluated as maximal exercise duration and oxygen consumption at peak exercise and anaerobic threshold. Peak oxygen consumption was calculated averaging the final 30 seconds of exercise. Anaerobic threshold was determined according to previous studies.[19–21] Before entry in the study, exercise tests were repeated at 2- to 3-day intervals up to the achievement of reproducible results (peak oxygen consumption change between 2 consecutive tests ≤1 ml/kg/min).

Blood samples for the determination of plasma norepinephrine and epinephrine concentrations were obtained at rest and peak exercise. Plasma catecholamine concentrations were measured by high-pressure liquid chromatography.

Protocol: A double-blind, parallel, randomized, placebo-controlled design was used. At entry in the study, patients were randomized into the following 2 treatment groups: placebo (n = 13) and ibopamine (n = 12). In the acute phase of the study, hemodynamic parameters, exercise capacity and plasma catecholamines were measured before and 1 hour after the administration of either placebo or ibopamine (100 mg). After completion of the acute phase, patients resumed their usual doses of digitalis, diuretics and vasodilators added to either placebo (1 tablet 3 times daily) or ibopamine (100 mg 3 times daily). All patients were followed up regularly every 2 weeks. Diuretic dosage was adjusted as clinically indicated by the evaluation of symptoms and body weight, whereas digitalis and vasodilator doses were kept constant. After 8 weeks of chronic therapy, patients were readmitted to the hospital to repeat the evaluation of hemodynamics, exercise capacity and plasma catecholamines. Baseline measurements were obtained 8 hours after the last dose of ibopamine or placebo and 1 hour after readministration. In both the acute and chronic studies, all other drugs were administered ≥12 hours before each evaluation, except vasodilators that were withheld ≥48 hours before.

Statistical analysis: Results are expressed as mean ± SD. Fisher's test was used to compare clinical data in the placebo and ibopamine groups; other data were analyzed by 2-way and repeated-measures analysis of variance; differences were considered significant at the $p < 0.05$ level. When analysis of variance indicated the presence of significant changes, Student's t test for paired samples with Bonferroni correction for multiple comparisons was used to identify the sources of differences and the significance of changes from values before drug administration.

RESULTS

Clinical follow-up: Because of the small number of patients studied, no significant difference was found between ibopamine- and placebo-treated patients in the clinical follow-up data. However, among the 12 patients treated with ibopamine, 4 improved clinically by 1 New York Heart Association functional class, 7 had no change, and 1 had a progressive deterioration of clinical status, which caused withdrawal from the study after 9 weeks. Among patients on placebo, 10 remained in stable clinical condition, 1 improved and 2 worsened by 1 functional class, and 1 was withdrawn from the study for development of severe heart failure. Furosemide dosage could be reduced by ≥25 mg in 4 patients on ibopamine, whereas it was kept constant in 7 and increased in 1. In contrast, diuretic dose was kept constant in 10 patients on placebo and increased in 3. Body weight remained stable in all patients, except those with worsening heart failure who were withdrawn from the study. No drug-related adverse effects occurred.

Resting hemodynamics (Table II): Acute ibopamine administration determined a 32% increase in cardiac index (2.09 ± 0.26 to 2.75 ± 0.43 liters/min/m^2) and a 25% increment of stroke volume index (24 ± 4 to 30 ± 4 ml/beat), with a concomitant, significant reduction in systemic vascular, total pulmonary and pulmonary vascular resistances (−23, −26 and −36%, respectively). Baseline values in the chronic study were similar to

those observed before acute drug administration. Chronic ibopamine readministration induced a 21% increment in cardiac index (2.33 ± 0.52 to 2.82 ± 0.62 liters/min/m^2) and a 20% increment in stroke volume index (29 ± 9 to 35 ± 9 ml/beat), with a decrease in systemic vascular (−16%), total pulmonary (−19%) and pulmonary vascular (−13%) resistances.

Peak exercise hemodynamics (Table III): Similar to the values at rest, after acute ibopamine ingestion, cardiac index had a 11% increase (4.90 ± 2.03 to 5.44 ±

TABLE II Effects of Placebo and Ibopamine on Resting Hemodynamics

	Acute Study		Chronic Study	
	Control	After Treatment	Control	After Treatment
Placebo group (n = 12)				
Heart rate (beats/min)	89 ± 21	88 ± 21	89 ± 20	88 ± 19
Mean arterial pressure (mm Hg)	93 ± 9	92 ± 6	94 ± 8	93 ± 8
Cardiac index (L/min/m^2)	2.22 ± 0.39	2.19 ± 0.55	2.27 ± 0.35	2.25 ± 0.40
Stroke volume index (ml/beats/min)	27.9 ± 6.83	25.5 ± 10.2	28.3 ± 5.6	27.9 ± 4.5
Stroke work index (g × cm^{-5} × m^2)	32.4 ± 10.2	29.6 ± 16.8	33.1 ± 9.9	32.7 ± 10.5
Systemic vascular resistance (dynes × s × cm^{-5})	1,641 ± 359	1,655 ± 323	1,589 ± 267	1,591 ± 233
Peripheral oxygen extraction (%)	35.7 ± 9.2	36.7 ± 7.9	35.2 ± 8.9	36.9 ± 7.7
Right atrial pressure (mm Hg)	7.5 ± 3.4	8.0 ± 3.2	8.8 ± 3.6	8.7 ± 3.2
Mean pulmonary pressure (mm Hg)	27.9 ± 9.0	27.8 ± 8.9	29.3 ± 11.2	25.9 ± 4.6
Pulmonary wedge pressure (mm Hg)	22.4 ± 9.5	22.6 ± 6.7	23.3 ± 9.5	21.1 ± 4.3
Total pulmonary resistance (dynes × s × cm^{-5})	446 ± 118	453 ± 104	447 ± 118	440 ± 104
Pulmonary vascular resistance (dynes × s × cm^{-5})	101 ± 55	87 ± 45	94 ± 50	88 ± 42
Ibopamine group (n = 11)				
Heart rate (beats/min)	88 ± 7	91 ± 9	81 ± 8	82 ± 12
Mean arterial pressure (mm Hg)	88 ± 6	87 ± 8	88 ± 7	90 ± 10
Cardiac index (L/min/m^2)	2.09 ± 0.26	2.75 ± 0.43*	2.33 ± 0.52	2.82 ± 0.62‡
Stroke volume index (ml/beats/min)	24 ± 4	30.3 ± 3.7*	29.4 ± 9.3	35.2 ± 9.4§
Stroke work index (g × cm^{-5} × m^2)	26.4 ± 10.4	43.4 ± 29.3	39.6 ± 29.8	36.4 ± 14.5
Systemic vascular resistance (dynes × s × cm^{-5})	1,631 ± 339	1,249 ± 245†	1,527 ± 332	1,287 ± 318§
Peripheral oxygen extraction (%)	36.2 ± 14.2	31.5 ± 8.7	38.1 ± 8.5	32.9 ± 6.4
Right atrial pressure (mm Hg)	10.1 ± 5.8	8.7 ± 4.8	8.4 ± 4.2	8.4 ± 4.1
Mean pulmonary pressure (mm Hg)	32.8 ± 11.9	31.6 ± 10.9	29.1 ± 10.3	30.3 ± 10.5
Pulmonary wedge pressure (mm Hg)	25.9 ± 10.9	25.2 ± 9.4	23.3 ± 9.6	23.6 ± 9.0
Total pulmonary resistance (dynes × s × cm^{-5})	684 ± 272	507 ± 173†	609 ± 282	488 ± 236†
Pulmonary vascular resistance (dynes × s × cm^{-5})	144 ± 54	106 ± 39†	120 ± 43	104 ± 44§

*p <0.001; †p <0.01 versus values before drug administration; ‡p <0.001; §p <0.01 versus values before drug administration of both acute and chronic studies.

TABLE III Effects of Placebo and Ibopamine on Peak Exercise Hemodynamics

	Acute Study		Chronic Study	
	Control	After Treatment	Control	After Treatment
Placebo group (n = 12)				
Heart rate (beats/min)	158± 18	157 ± 17	159 ± 16	157 ± 17
Mean arterial pressure (mm Hg)	111 ± 11	110 ± 8	111 ± 10	109 ± 9
Cardiac index (L/min/m^2)	5.17 ± 2.27	5.3 ± 2.6	5.21 ± 2.31	5.32 ± 2.71
Stroke volume index (ml/beats/min)	32.5 ± 12.9	33.3 ± 15.7	32.6 ± 13.6	33.6 ± 16.1
Stroke work index (g × cm^{-5} × m^2)	42.7 ± 30.5	43.0 ± 30.9	42.3 ± 30.1	42.6 ± 31.6
Systemic vascular resistance (dynes × s × cm^{-5})	921 ± 306	921 ± 353	912 ± 314	896 ± 312
Peripheral oxygen extraction (%)	66.9 ± 8.9	67.2 ± 9.4	67.0 ± 9.2	66.7 ± 9.2
Right atrial pressure (mm Hg)	10.9 ± 5.0	10.8 ± 4.6	11.5 ± 4.3	11.6 ± 4.2
Mean pulmonary pressure (mm Hg)	48.0 ± 9.9	47.6 ± 9.8	48.7 ± 9.4	47.8 ± 9.2
Pulmonary wedge pressure (mm Hg)	40.9 ± 10.0	40.7 ± 10.0	41.1 ± 9.7	40.7 ± 9.9
Total pulmonary resistance (dynes × s × cm^{-5})	447 ± 212	418 ± 215	456 ± 219	421 ± 205
Pulmonary vascular resistance (dynes × s × cm^{-5})	80 ± 45	76 ± 41	85 ± 44	77 ± 39
Ibopamine group (n = 11)				
Heart rate (beats/min)	142 ± 18	146 ± 29	144 ± 24	141 ± 24
Mean arterial pressure (mm Hg)	103 ± 13	102 ± 13	108 ± 19	105 ± 13
Cardiac index (L/min/m^2)	4.90 ± 2.03	5.44 ± 1.99*	5.11 ± 1.47	6.13 ± 1.68†
Stroke volume index (ml/beats/min)	35.1 ± 16.5	37.7 ± 12.9	35.9 ± 10.4	44.7 ± 14.9†
Stroke work index (g × cm^{-5} × m^2)	45.6 ± 33.8	49.9 ± 35.0	48.6 ± 33.1	61.3 ± 40.6†
Systemic vascular resistance (dynes × s × cm^{-5})	857 ± 304	735 ± 209*	787 ± 153	660 ± 127†
Peripheral oxygen extraction (%)	69.2 ± 11.0	62.0 ± 8.2	65.0 ± 7.7	62.3 ± 10.6
Right atrial pressure (mm Hg)	15.3 ± 7.2	15.3 ± 7.4	15.4 ± 7.8	15.8 ± 7.5
Mean pulmonary pressure (mm Hg)	53.0 ± 16.8	51.1 ± 15.8	49.6 ± 13.6	48.3 ± 14.1
Pulmonary wedge pressure (mm Hg)	45.0 ± 13.3	43.4 ± 12.7	41.8 ± 10.5	38.2 ± 14.9
Total pulmonary resistance (dynes × s × cm^{-5})	497 ± 293	480 ± 251	454 ± 227	413 ± 252
Pulmonary vascular resistance (dynes × s × cm^{-5})	97 ± 61	82 ± 46	81 ± 46	83 ± 54

*p <0.05 versus values before drug administration; †p <0.05 versus values before drug administration of both acute and chronic studies.

1.99 liters/min/m^2), with a concomitant 14% reduction in systemic vascular resistance (858 ± 304 to 735 ± 209 dynes × s × cm^{-5}); there was no significant change in the other hemodynamic parameters. After chronic therapy, peak exercise hemodynamics before drug readministration were not significantly different from those at baseline in the acute study. After ibopamine readministration, peak exercise cardiac, stroke volume and stroke work indexes increased by 20, 24 and 26%, respectively, with a 16% decrease in systemic vascular resistance.

Exercise capacity (Figure 1): Ibopamine therapy did not significantly change exercise capacity in comparison with placebo, although oxygen consumption at peak exercise and anaerobic threshold increased ≥1 ml/kg/min in 3 patients on ibopamine and in none on placebo.

Plasma catecholamines (Figure 2): In comparison with placebo, ibopamine therapy significantly reduced both resting and exercise plasma norepinephrine; plasma epinephrine was not significantly changed.

Resting plasma norepinephrine averaged 733 ± 245 pg/ml at baseline and decreased by 40% (438 ± 157 pg/ml) after acute ibopamine. After chronic therapy, plasma norepinephrine was significantly reduced, in comparison with control values of the initial study, also before drug administration (544 ± 227 pg/ml), with a further decrease after ibopamine readministration (384 ± 145 pg/ml). Similar to the results obtained at rest,

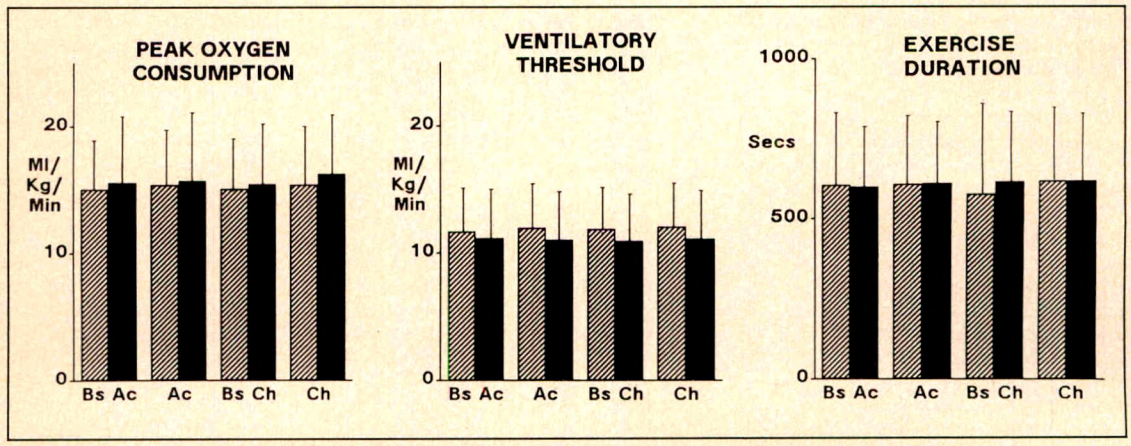


FIGURE 1. Effects on exercise capacity of acute and chronic placebo *(dashed bars)* and ibopamine *(black bars)* administration. Ac = effects of acute drug administration; Bs Ac = baseline of acute study; Bs Ch = baseline of chronic study; Ch = effects of drug readministration.

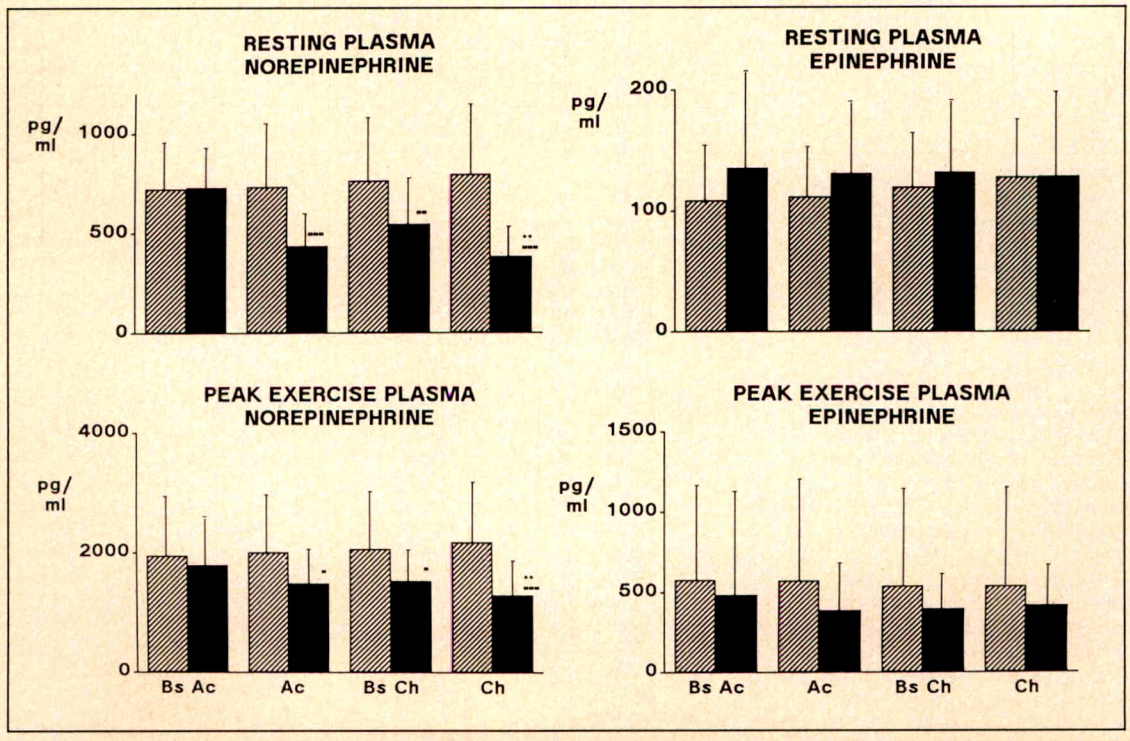


FIGURE 2. Effects on resting and peak exercise plasma catecholamines of acute and chronic placebo *(dashed bars)* and ibopamine *(black bars)* administration. *p <0.05; **p <0.01; and ***p <0.001 versus values before drug administration (baseline); ++p <0.01 versus values before drug administration of chronic study. Abbreviations as in Figure 1.

peak exercise plasma norepinephrine decreased (1,796 ± 783 to 1,497 ± 552 pg/ml) after acute ibopamine ingestion, was still significantly reduced (1,534 ± 520 pg/ml) after chronic therapy and further decreased (1,294 ± 569 pg/ml) after ibopamine readministration.

DISCUSSION

The results show that acute and chronic ibopamine administration determines (both at rest and during exercise) a significant increase in cardiac and stroke volume indexes accompanied by a reduction in systemic, total pulmonary and pulmonary vascular resistances. These hemodynamic effects can be attributed to activation of dopamine 1 and 2, β-2 and (to a lesser extent) β-1 receptors.[5] Stimulation of dopamine 1 receptors determines selective dilatation of renal, splanchnic, coronary and cerebral vascular beds; stimulation of dopamine 2 and β-2 receptors induces generalized vasodilation through inhibition of norepinephrine release from sympathetic nerve endings and relaxation of vascular smooth muscle, respectively.[1-3] Peripheral vasodilation can at least partially account for the improvement in cardiac index observed after ibopamine. Activation of β-1 receptors can further contribute to this effect; however, the number and sensitivity of β-1 receptors is reduced in congestive heart failure,[22] and ibopamine at the dose we used does not appear to have major effects on myocardial contractility.[5,9,23]

This study shows that the acute hemodynamic effects of ibopamine were also maintained during long-term therapy, with no evidence of tolerance development. The data are in agreement with other studies,[11-14,24] but differ from a previous one in which tolerance was observed[10]; however, in the latter study, ibopamine dosages were greater than in our study (200 mg 3 times daily in 4 patients, and 300 mg 3 times daily in 5 of 10 studied patients). At these doses, ibopamine has a more potent activity on postsynaptic α-adrenergic receptors,[5] which can explain the discrepancies with our results.

In the present study, ibopamine administration did not significantly improve exercise capacity. Similar data were obtained in previous reports,[10,11] whereas in 2 large, multicenter, placebo-controlled studies, exercise capacity was significantly increased.[12,14] This discrepancy can be explained by our smaller study group and brief duration of follow-up.

Increased plasma norepinephrine levels are known to be an unfavorable prognostic index in patients with congestive heart failure.[25,26] In this study, ibopamine induced a significant decrease in both resting and peak exercise plasma norepinephrine levels; after chronic therapy, the decrease in plasma norepinephrine was still present before ibopamine readministration, with a further decrease after drug ingestion. The data confirm and extend previous results.[10,27] This effect of ibopamine can be explained by reflex reduction of sympathetic activity due to the hemodynamic improvement; however, other agents, such as levodopa, which induce similar hemodynamic changes but have a partially different mechanism of action,[28] were shown to increase rather than reduce plasma norepinephrine.[29] Thus, the decrease in sympathetic activity after ibopamine can be ascribed to the inhibition of norepinephrine release from sympathetic nerve endings induced by activation of dopamine 2 and α-2 receptors. This effect can contribute to the peripheral vasodilating activity of this drug and, furthermore, can explain its good tolerability and lack of arrhythmogenicity.[27,30]

Acknowledgment: We gratefully acknowledge Chiara Pioselli for invaluable help in the preparation of this manuscript.

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Exclusion of Coronary Artery Disease by Exercise Thallium-201 Tomography in Patients with Aortic Valve Stenosis

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In many patients with valvular aortic stenosis (AS), management decisions may be possible without invasive studies if coexistent coronary artery disease (CAD) can be ruled out noninvasively. The use of thallium-201 single-photon emission computed tomography to the exclusion of CAD was studied in 44 patients aged 41 to 78 years with AS. In addition to cardiac catheterization and selective coronary angiography, patients underwent a cardiac ultrasound study and thallium-201 myocardial perfusion imaging at rest and after bicycle ergometer exercise. Two thirds of the patients had critical AS (valve area index ≤0.5 cm^2/m^2) but none had left ventricular systolic dysfunction. Twenty-one patients had angiographically significant CAD (≥50% diameter stenosis in ≥1 coronary artery), whereas 23 had either a fully normal angiogram (n = 17) or mild (<50%) stenoses (n = 6). Each patient with significant CAD had an abnormal thallium-201 tomogram, either a strictly segmental perfusion defect (n = 19), or a patchy nonsegmental abnormality (n = 2); however, 10 of 23 patients free of significant CAD had similar results. Thus, the sensitivity and specificity of an abnormal scintigram were 100 and 57%, respectively. If only segmental perfusion defects typical of CAD had been considered abnormal, then the sensitivity of the test would have been 90% and the specificity 70%. Patients with false abnormal scintigrams had more severe AS and more angiographically nonsignificant CAD than those with true normal findings. It is concluded that a fully normal exercise thallium-201 tomogram excludes angiographically significant CAD in patients with AS, and that false-positive findings are related to critical valve area reduction and to the presence of mild coronary stenoses.

(Am J Cardiol 1992;70:635–640)

From the Division of Cardiology, First Department of Medicine, Helsinki University Central Hospital, Helsinki, Finland. This study was supported by Paavo Nurmi Foundation, Helsinki, Finland. Manuscript received February 14, 1992; revised manuscript received and accepted May 18, 1992.

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Recent developments in Doppler echocardiography have realized a fully noninvasive assessment of the severity of valvular aortic stenosis (AS).[1] Provided that coexistent coronary artery disease (CAD) could be excluded without angiography, management decisions could be made without cardiac catheterization in a significant proportion of patients. The use of thallium-201 scintigraphy has been studied in this respect in a few centers,[2–6] but the results have not been very encouraging,[2,3,6] except in 1 institution.[4,5] All these studies used planar imaging and involved only small numbers (9 to 27) of patients with predominant AS. In the present investigation, we have extended this approach by studying the usefulness of thallium-201 single-photon emission computed tomography in a larger series of patients undergoing diagnostic cardiac catheterization because of AS.

METHODS

Patients: Forty-eight patients undergoing cardiac catheterization because of AS were studied between March 1990 and April 1991 at our institution. They constituted a consecutive series of patients having AS with or without clinical suspicion of CAD, except that those with (1) emergency catheterization, (2) overt congestive heart failure, or (3) clinical signs of more than mild aortic regurgitation, were excluded. For technical reasons, either selective coronary angiography or thallium-201 tomography could not be performed in 4 patients, and the final study group thus consisted of 44 persons: 23 men and 21 women aged 41 to 78 years (mean 63). All had dyspnea or chest pain on effort. One patient had a history of myocardial infarction and another had had episodes of unstable angina pectoris. Forty-two patients had sinus rhythm and 2 had atrial fibrillation. Two patients had a left bundle branch block on the electrocardiogram. In all, 34 patients were receiving cardioactive drugs: digoxin (n = 16), long-acting nitrates (n = 16), β-adrenoceptor blocking agents (n = 14), calcium antagonists (n = 13), and diuretics (n = 12).

Study aims and protocol: The primary aim of the present study was to evaluate whether exercise thallium-201 tomography could be used to exclude clinically significant CAD in patients with symptomatic AS. Our second aim was to identify factors responsible for eventual false-positive or negative scintigraphic findings with respect to the presence of CAD. The protocol included (1) left and right-sided cardiac catheterization with se-

lective coronary angiography, aortic root cineangiography and an optional left ventricular cineangiography; (2) a combined 2-dimensional, M-mode and Doppler echocardiography; and (3) a thallium-201 exercise test. A magnetic resonance imaging study of the aortic valve was also performed but the data will be reported elsewhere. The noninvasive studies were done 1 day to 1 week preceding catheterization. The patients continued to take their regular medication throughout the hospital stay, including the days of catheterization and thallium exercise testing. The study protocol was reviewed and approved by the institutional ethics committee.

Catheterization and angiography: A complete left- and right-sided cardiac catheterization was performed in the standard way. Pressures were recorded through fluid-filled catheters with Statham P23 transducers using the midaxillary line as the zero reference level. The aortic valve was crossed in retrograde fashion. The mean systolic transvalvular gradient and the duration of the systolic period were derived from pullback pressure recordings: 3 pairs of ventricular and aortic pressure cycles with equal preceding QQ intervals were analyzed and averaged for the data. Cardiac output was determined as the average of 5 measurements obtained by thermodilution. The aortic valve area was calculated by the Gorlin formula.[7] Cardiac output and aortic valve area were normalized by dividing with body surface area.

Coronary angiography was performed using 6Fr high-flow Judkins or Amplatz catheters and filming in multiple projections including caudal and cranial views. The studies were interpreted visually by experienced angiographers unaware of the results of thallium scintigraphy. A luminal diameter reduction ≥50% in ≥1 coronary artery was considered significant CAD. Stenoses were recorded separately in the proximal part and in the middle and distal parts (combined) of the left anterior descending, left circumflex and right coronary arteries as well as in the largest diagonal and left obtuse marginal branches. Segments before the first diagonal, first obtuse marginal and the largest right ventricular branches were considered proximal in the left anterior descending, left circumflex and right coronary arteries, respectively. Aortic root angiography was performed and interpreted in the standard way to evaluate aortic regurgitation.[8] Left ventricular cineangiography was performed in only a few patients, and these studies are therefore not reported.

Echocardiography: The echocardiographic and Doppler studies were performed with a Toshiba SSH 160A ultrasonograph. Aortic valve area was determined using the continuity equation.[9] Left ventricular end-diastolic dimension, fractional shortening, and the thicknesses of interventricular septum and posterior wall were determined on M-mode recordings by the 2-dimensional parasternal long-axis view.[10] Fractional shortening <24% was considered abnormal.[10] Left ventricular mass was calculated from the leading edge-to-leading edge measurements using the cube formula[11] and the following regression equation[12]: Left ventricular mass (g) = 0.80 × (cube left ventricular mass) + 0.6. The data were normalized to body surface area. Left ventricular hypertrophy was diagnosed when mass index was >134 g/m^2 in men and >110 g/m^2 in women.[13]

Exercise thallium-201 tomography: Forty-three patients performed bicycle exercise to a symptom-limited end point or to >85% of their age-predicted maximal heart rate. The initial external work load was 50 W for 4 minutes. Thereafter, the load was increased every 4 minutes by 25 W in women and by 50 W in men until the stopping criteria were fulfilled. At peak exercise, a dose of 3 mCi of thallium-201 was administered intravenously, and the patient continued to exercise for 1 additional minute. Because of the inability to exercise, 1 patient was given an intravenous injection of 0.5 mg/kg of dipyridamole within 2 minutes, and thallium-201 was administered 3 minutes later. The Mason-Likar modification of the standard 12-lead electrocardiogram was recorded at rest and at 1-minute intervals both during exercise and over a 5-minute postexercise period. The peak ST-segment shift in the anterior leads during or after exercise was noted.

The scintigraphic imaging was begun 10 to 15 minutes after cessation of exercise. Elscint Apex 415 ECT equipment was used for single-photon emission computed tomography. Thirty views were obtained at 6° intervals within 20 minutes using a low-energy all-purpose collimator (Elscint APC-3). The redistribution image was obtained 3 hours later. Routine uniformity and center of rotation checks were performed regularly. The data were acquired using a 64 × 64 matrix.

The image reconstruction was performed by a minicomputer (Apex F1, Elscint). Significant upward creep was excluded by inspecting the raw data.[14] Transaxial and oblique slices of the heart as well as polar bull's-eye maps[15] were then generated. Visual analysis of the slices and maps was performed by 1 experienced investigator responsible for all isotope studies in our laboratory. The assessment was made without any knowledge of findings at cardiac catheterization or echocardiography. To help visual analysis, a semiquantitation of the bull's-eye image was done using a graded color scale. Each separate color indicated a 10% change in counts. The images were normalized so that the maximal pixel was at the 100% point. In addition, an image of thallium-201 washout was generated by subtracting, pixel by pixel, the activity in the redistribution map from the activity in the postexercise map and dividing the difference by the activity in the postexercise map. The studies were considered abnormal if they showed (1) strictly segmental defects with or without redistribution (abnormal, CAD likely); or (2) nonsegmental diffuse or patchy changes with significant intensity reductions in the defects (abnormal, CAD unlikely). Figure 1A shows a normal thallium-201 tomographic study and Figure 1B and C examples of segmental and patchy abnormalities.

Statistical analysis: Comparisons between means of measurements of independent data were performed with Student's *t* test. The frequency data were analyzed in 2 × 2 tables using Fisher's exact test. The diagnostic sensitivity and specificity of exercise thallium-201 tomography in detecting angiographically significant CAD were

calculated in the conventional way. Two-tailed p values <0.05 were considered statistically significant. Numerical data are given as mean ± standard deviation.

RESULTS

Hemodynamic and angiographic characteristics of the study population: The aortic valve area index, determined invasively in 37 patients and by Doppler echocardiography in 7, averaged 0.48 cm^2/m^2 (range 0.18 to 1.43 cm^2/m^2) and was ≤0.5 cm^2/m^2 in 29 persons (66%). The range of mean systolic transvalvular pressure gradient was 4 to 129 mm Hg (average 57), and the range of cardiac index, 1.5 to 4.9 liters/min/m^2 (mean 2.5). The pulmonary capillary wedge pressure averaged 9 mm Hg (range 1–31); 4 patients had a value >14 mm Hg. Aortic root angiography revealed mild transvalvular regurgitation (1-2/4) in 25 patients. At echocardiography, only 1 patient had left ventricular end-diastolic diameter >60 mm (mean 47), and all had fractional shortening ≥24% (mean 37). Left ventricular mass index ranged from 81 to 230 g/m^2 (mean 152), and 36 patients (82%) had left ventricular hypertrophy. These data indicate that the majority of patients we studied had critical AS with concentric left ventricular hypertrophy, normal systolic ventricular function and little or no pulmonary venous congestion at rest.

At coronary angiography, 21 patients (48%) had 1 or more coronary artery stenoses ≥50% of the luminal diameter. Six of them had 3-vessel CAD (3 also had left main stenosis), 6 had 2-vessel CAD and 9 had 1-vessel CAD. In 8 patients, significant stenoses were found only beyond the proximal parts of the major coronary arteries. The remaining 23 patients had either completely normal angiograms (n = 17) or mild (<50%) stenoses (n = 6).

Comparison of aortic stenosis patients with and without significant coronary artery disease: Table I compares the clinical, invasive and echocardiographic data in AS patients with and without coexistent significant CAD. Patients with CAD were older and had lower fractional shortening; otherwise, there were no significant differences between the groups.

Results of exercise thallium-201 tomography: No complications related to the exercise test occurred. Table II compares the exercise data in patients with and without angiographically significant CAD, and Table III summarizes the findings at thallium-201 tomography. Every patient with angiographically significant CAD had abnormal thallium-201 tomograms, and 10 of 23 patients free of significant CAD also had these results. Thus, an abnormal scintigram had a sensitivity of 100% and a specificity of 57% in detecting angiographi-

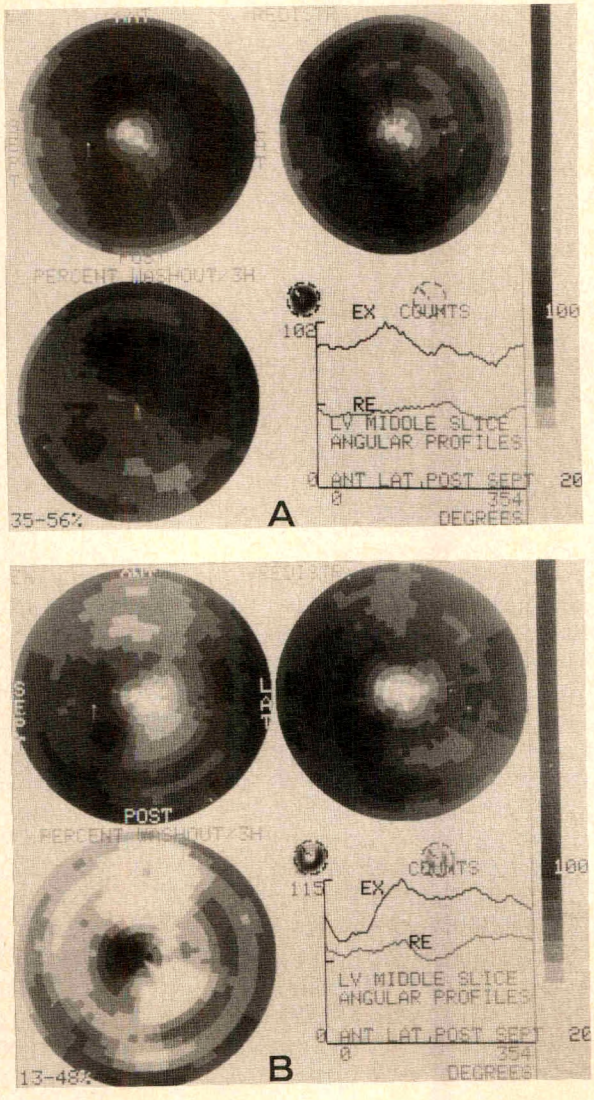


FIGURE 1. Examples of thallium-201 tomography in patients with aortic valve stenosis. In each figure *(A to C)*, bull's eye maps are shown after exercise *(above left)* and after a 3-hour redistribution *(above right)*. The third map *(bottom left)* shows the percent washout of thallium-201 pixel by pixel over the 3-hour period. Each map is normalized to 100% at its maximal pixel activity. The shade of the *grey scale* changes after every 10% change in isotope activity. *A*, a normal isotope distribution and washout; *B*, a segmental anteroapical defect with redistribution; and *C*, patchy diffuse defects in isotope activity. ANT = anterior; EX = exercise; LAT = lateral; LV = left ventricular; POST = posterior; REDISTR = redistribution; SEPT = septal.

TABLE I Clinical, Invasive and Echocardiographic Characteristics of Patients Having Valvular Aortic Stenosis With or Without Angiographically Significant Coronary Artery Disease

Characteristic	With CAD (n = 21)	Without CAD (n = 23)	p Value*
Clinical			
Mean age (years)	65 ± 9	60 ± 8	0.034
Men/women	13/8	10/13	0.246
Angina pectoris	10	11	0.891
Functional class			
NYHA I to II	7	13	
NYHA III	14	10	0.143
Catheterization			
Right atrial pressure (mm Hg)	4 ± 2	4 ± 3	0.326
Pulmonary artery systolic pressure (mm Hg)	27 ± 8	25 ± 12	0.520
Pulmonary artery wedge pressure (mm Hg)	9 ± 6	8 ± 7	0.890
LV peak systolic pressure (mm Hg)	191 ± 36	213 ± 52	0.136
LV end-diastolic pressure (mm Hg)	14 ± 6	18 ± 11	0.164
Mean systolic LV-aortic gradient (mm Hg)	50 ± 27	64 ± 34	0.196
Cardiac index (liters/min/m^2)	2.6 ± 0.7	2.5 ± 0.5	0.683
Aortic valve area index (cm^2/m^2)†	0.54 ± 0.37	0.43 ± 0.24	0.175
Echocardiography			
LV end-diastolic diameter (mm)	48 ± 6	47 ± 9	0.559
LV fractional shortening (%)	34 ± 7	39 ± 8	0.024
LV mass index (g/m^2)	154 ± 35	151 ± 39	0.739

*The p values are from Student's *t* test or Fisher's exact test.
†Valve area was measured by Doppler in 4 patients with and 3 patients without coronary artery disease.
Data are mean ± standard deviation.
CAD = coronary artery disease; LV = left ventricular; NYHA = New York Heart Association.

TABLE II Findings at Exercise Stress Test in Patients with Aortic Valve Stenosis Undergoing Thallium-201 Tomography

Exercise Characteristic	With CAD (n = 21)	Without CAD (n = 23)	p Value
Peak heart rate (beats/min)	117 ± 21	135 ± 21	0.009
Peak systolic blood pressure (mm Hg)	161 ± 28	161 ± 21	0.955
Peak work load (W)	90 ± 34	97 ± 37	0.564
Exercise duration (s)	436 ± 175	511 ± 184	0.176
ST-segment depression (mm)*	2.7 ± 1.5	1.3 ± 1.0	0.001
Angina pectoris (no. of pts)	9	8	0.751

*Maximal electrocardiographic ST-segment depression during or after exercise.
Data are mean ± standard deviation.
CAD = coronary artery disease.

cally significant coronary stenoses. The specificity was 44% in 29 patients with critical AS (valve area index ≤0.5 cm^2/m^2) and 86% in 15 patients with noncritical AS (valve area index >0.5 cm^2/m^2) (p = 0.089).

Among the 31 patients with abnormal scintigrams, 26 had segmental perfusion defects typical of CAD and 5 had patchy nonsegmental abnormalities (see Table III). The sensitivity and specificity of a strictly segmental perfusion defect were 90 and 70%, respectively, in detecting angiographically significant CAD. Sensitivity was 85% in patients with critical AS and 100% in those with noncritical valve area reduction. Specificity was 63% in the former group and 86% in the latter. The 2 patients with CAD and a nonsegmental thallium abnormality both had critical AS (valve areas, 0.38 and 0.44 cm^2/m^2) combined with ≥80% stenosis in the proximal left anterior descending artery. Neither patient achieved a heart rate >95 beats/min at the exercise test.

Abnormal thallium-201 tomography in patients free of significant coronary artery disease: Among patients free of significant CAD, 13 had a fully normal thallium-201 tomogram and 10 had abnormal scintigrams. Table IV shows that patients with an abnormal scintigram had more severe AS and a clear trend toward more marked left ventricular hypertrophy. Furthermore, 5 of 10 patients with scintigraphic abnormalities had altogether 8 angiographically nonsignificant coronary stenoses (20 to 40%); however, there was only 1 mild narrowing (30%) in 1 of 13 patients with normal perfusion imaging (p = 0.052). There were no comparable differences either in age or sex, or in symptoms, heart rate, systolic blood pressure, work load, or ST-segment shift at the end of exercise.

DISCUSSION

The main findings of our study were: (1) A fully normal exercise thallium-201 tomography reliably excludes angiographically significant CAD in patients with AS. (2) The specificity of this test is dependent on the severity of valve disease and possibly also on the

presence of angiographically nonsignificant coronary artery narrowings.

Efficacy of thallium-201 tomography in excluding coronary artery disease: Throughout the present study, our main interest was in the performance of exercise thallium-201 tomography to the exclusion of, rather than in the detection of, angiographically significant CAD in patients with AS. Given a normal thallium-201 scintigram, the probability of the absence of CAD is related both to the sensitivity and specificity of an abnormal result and, in addition, to the prevalence of CAD in the population.[16] A reliable exclusion of CAD needs high sensitivity in particular. In previous studies of patients with predominant AS,[2–5] the sensitivity of exercise[2–4] or dipyridamole[5] thallium-201 scintigraphy varied from 5 of 7 to 11 of 13 patients in detecting coronary diameter stenoses >50%[3–5] or >70%.[2] The higher proportion of false-negative findings compared with our study may have been due to the planar imaging technique but probably even more to the stricter criteria for a positive thallium scintigram: only segmental perfusion defects were considered abnormal.[2–5] We used broader criteria in the present study because the false-negative findings in these earlier studies had clearly shown that the perfusion image can be abnormal in patients with AS and coexistent CAD without showing typical segmental defects. If such defects only had been considered abnormal in our study, the method would have missed critical stenoses of the proximal left anterior descending artery in 2 patients, even though the overall sensitivity would still have remained high (90%).

False abnormal findings: The cost of reliably excluding angiographically significant CAD by a fully normal thallium tomogram was the relatively poor specificity of an abnormal test result. In previous investigations, the specificity of thallium scintigraphy in predominant AS ranged from 3 of 11 to 9 of 9 patients.[2,4] Apical perfusion defects often have been false-positive,[2,3] and they have been included among normal findings in some studies.[4,5] In our study, 6 of 10 patients with false abnormal scintigrams had apical perfusion defects, but in none was the defect localized to the apex alone.

TABLE III Summary of Findings at Exercise Thallium-201 Tomography in Patients Having Valvular Aortic Stenosis With or Without Angiographically Significant Coronary Artery Disease

	No.of Patients	Normal Thallium-201 Tomography	Abnormal Thallium-201 Tomography	
			CAD Likely	CAD Unlikely
With CAD	21	0	19	2
Without CAD	23	13	7	3

CAD = coronary artery disease (≥ 50% diameter stenosis in ≥ 1 coronary artery).

Patients with abnormal scintigrams in the absence of significant CAD had more severe AS, a higher left ventricular free wall thickness and a trend toward higher end-diastolic pressure at rest. They also had more mild coronary artery narrowings than those with fully normal thallium-201 tomograms. It is likely that even in these patients the perfusion defects reflected true myocardial ischemia although not angiographically significant CAD. Combined with severe hypertrophy and high left ventricular systolic pressure, even mild coronary stenoses may become functionally significant on effort. The reasons for this are the very high myocardial oxygen demand and the reduction of coronary perfusion pressure and flow time due to delayed relaxation and increased diastolic pressure of the left ventricle.[17]

Clinical implications: In translating our results into clinical practice, the characteristics of our group with AS must be kept in mind. We studied patients of whom half had significant CAD and two thirds had critical AS. In such a population, according to our data, significant CAD could be reliably excluded with exercise thallium-201 tomography in about 30%. However, the pro-

TABLE IV Invasive and Echocardiographic Findings in Relation to Results of Thallium-201 Tomography in Patients Having Valvular Aortic Stenosis Without Angiographically Significant Coronary Artery Disease

Measurement	Tomography		p Value
	Normal Tl-201 (n = 13)	Abnormal Tl-201 (n = 10)	
Catheterization			
Pulmonary artery wedge pressure (mm Hg)	8 ± 7	7 ± 7	0.605
LV peak systolic pressure (mm Hg)	191 ± 47	245 ± 42	0.011
LV end-diastolic pressure (mm Hg)	15 ± 5	23 ± 12	0.080
Mean systolic LV-aortic gradient (mm Hg)	50 ± 35	80 ± 26	0.044
Cardiac index (liters/min/m^2)	2.5 ± 0.5	2.4 ± 0.5	0.529
Aortic valve area index (cm^2/m^2)	0.51 ± 0.28	0.32 ± 0.12	0.046
Echocardiography			
LV end-diastolic diameter (mm)	45 ± 9	49 ± 8	0.348
Posterior wall thickness (mm)	13 ± 2	15 ± 2	0.046
Interventricular septal thickness (mm)	13 ± 3	15 ± 3	0.304
LV mass index (g/m^2)	137 ± 39	170 ± 34	0.052
Fractional shortening (%)	41 ± 8	36 ± 8	0.134

Data are mean ± standard deviation.
LV = left ventricular; Tl-201 = thallium-201.

portion of patients who are able to undergo surgery without angiography would probably be smaller (close to 20%), because in some patients recommended to follow-up owing to noncritical AS and normal thallium tomography, the scintigram might change to abnormal with the progression of AS. In AS populations with different prevalences of critical stenosis and significant CAD, the above percentages would be different.

We admit that the safety of exercise testing in symptomatic AS can be questioned.[18] Our patients had no complications, however, and other recent studies also support the safety and feasibility of carefully supervised exercise tests in patients with AS.[19,20] We also acknowledge that one may question whether knowing the coronary anatomy is at all necessary in patients with critical AS, since the benefits of combining myocardial revascularization with valve replacement have not been proved in a randomized study.[21,22] However, routine bypass of significant coronary stenoses is current practice in most centers, and coronary angiography therefore remains an essential part of patient evaluation. Our study shows that exercise thallium-201 tomography may be a useful adjunctive method in assessing these patients because a fully normal scintigram excludes angiographically significant CAD. These findings (especially if confirmed in a larger study) should help clinicians make management decisions without cardiac catheterization in a significant proportion of patients with AS.

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Immediate Effects of Percutaneous Transvenous Mitral Commissurotomy on Pulmonary Hemodynamics at Rest and During Exercise in Mitral Stenosis

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Hemodynamics were evaluated during exercise in 33 patients with mitral stenosis who underwent percutaneous transvenous mitral commissurotomy (PTMC). PTMC was performed using an Inoue balloon. Each patient underwent a supine ergometer exercise test before and on the day after PTMC. Ergometer work load was started at 20 W and increased in increments of 20 W at 3-minute intervals until terminated by the patient's fatigue or shortness of breath. Mitral valve area increased by 0.8 ± 0.4 cm² (1.1 ± 0.3 to 1.9 ± 0.4 cm², p <0.001). Mean mitral pressure gradient decreased (12 ± 5 to 6 ± 2 mm Hg, p <0.001). Pulmonary arterial pressure significantly decreased and the cardiac index significantly increased both at rest and during exercise after PTMC. Before PTMC, the increases in pulmonary arterial pressure, total pulmonary resistance and pulmonary arteriolar resistance during exercise were greater in patients with a mitral valve area <1.0 cm² than in patients with an area ≥1.0 cm². After PTMC, total pulmonary resistance still increased during exercise. However, pulmonary arteriolar resistance did not change during exercise in patients with a mitral valve area ≥1.5 cm², whereas it increased in patients with an area <1.5 cm². An enlarged mitral valve area ≥1.5 cm², which may prevent pulmonary vasoconstriction and permits a greater increase in pulmonary blood flow during exercise, is considered a good result immediately after PTMC.

(Am J Cardiol 1992;70:641–644)

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Recently, percutaneous transvenous mitral commissurotomy (PTMC), first reported by Inoue et al,[1] has been established as an alternative to surgery in mitral stenosis. Patients with a mitral valve area <1.5 cm² may complain of dyspnea on mild exertion or at rest[2–6] depending on the degree of mitral stenosis.

We present an analysis of hemodynamics during exercise and the effects of PTMC in patients with mitral stenosis.

METHODS

Patients: The study comprised 33 patients (9 men and 24 women aged 48.2 ± 10.3 years) with mitral stenosis who underwent PTMC between 1989 and 1991. Thirteen patients were in normal sinus rhythm and 20 had atrial fibrillation.

Supine ergometer exercise test: Each patient underwent a symptom-limited (leg fatigue or shortness of breath) supine ergometer exercise test during right-sided cardiac catheterization before and on the day after PTMC with use of a thermodilution catheter (REF-1 catheter, American Edwards). Heart rate, pulmonary arterial pressure, cardiac output by the thermodilution technique and systemic blood pressure were obtained at rest and during exercise (systemic blood pressure was measured using a sphygnomanometer by the same examiner both before and after PTMC). Ergometer work load was begun at 20 W and increased in increments of 20 W at 3-minute intervals until terminated by the patient's symptoms.

Percutaneous transvenous mitral commissurotomy: A thermodilution catheter, which had been located in the pulmonary artery since the day before PTMC, was used for monitoring pulmonary arterial pressure and cardiac output. PTMC was performed as previously described[1,7] using an Inoue balloon. The balloon catheter was introduced through the punctured atrial septum midway into the mitral orifice, and inflated. Gorlin's formula was used for calculation of mitral valve area.[8]

Student's *t* test was used for statistical analysis. All data are reported as mean ± SD, and a p value <0.05 was considered significant.

RESULTS

Hemodynamic improvement and complications: Mitral valve area was increased by 0.8 ± 0.4 cm² (1.1 ±

TABLE I Hemodynamic Data at Rest and During Exercise Before and After Percutaneous Transvenous Mitral Commissurotomy

	Before PTMC				After PTMC		
	Rest	20 W	40 W	60 W	Rest	20 W	40 W	60 W
Pulmonary arterial pressure (mm Hg)								
Systolic	40 ± 13	64 ± 18	73 ± 17	81 ± 16	35 ± 8*	52 ± 13*	62 ± 14*	71 ± 13*
Diastolic	18 ± 8	31 ± 11	36 ± 11	40 ± 12	14 ± 5*	23 ± 7*	28 ± 7*	33 ± 7*
Mean	25 ± 9	42 ± 13	50 ± 15	54 ± 12	22 ± 6*	32 ± 10*	40 ± 10*	45 ± 8*
Total pulmonary vascular resistance (dynes s cm^{-5}/m^2)	736 ± 335	914 ± 426	819 ± 332	834 ± 328	522 ± 183*	571 ± 213*	550 ± 195†	526 ± 101‡
Pulmonary arteriolar resistance (dynes s cm^{-5}/m^2)	212 ± 88	241 ± 102	210 ± 62	230 ± 67	171 ± 59†	177 ± 71*	158 ± 53*	172 ± 64‖
Cardiac index (liters/min/m^2)	3.0 ± 0.7	4.0 ± 0.9	4.8 ± 0.9	5.3 ± 0.9	3.4 ± 0.7*	4.8 ± 1.4§	5.7 ± 1.3*	6.5 ± 1.0*
Systemic blood pressure (mm Hg)								
Systolic	122 ± 16	135 ± 21	142 ± 21	147 ± 21	117 ± 12	129 ± 18‖	140 ± 20	148 ± 23
Diastolic	71 ± 12	80 ± 13	82 ± 12	84 ± 13	70 ± 11	76 ± 12	81 ± 11	83 ± 12
Mean	88 ± 12	98 ± 15	103 ± 12	106 ± 12	86 ± 10	94 ± 13	102 ± 14	103 ± 13
Systemic vascular resistance (dynes s cm^{-5}/m^2)	2,469 ± 709	2,078 ± 600	1,703 ± 433	1,622 ± 341	2,050 ± 484*	1,645 ± 415*	1,423 ± 405*	1,319 ± 342*

*$p < 0.001$; †$p < 0.005$; ‡$p < 0.01$; §$p < 0.02$; ‖$p < 0.05$: parameters were compared with those before PTMC.
PTMC = percutaneous transvenous mitral commissurotomy.

0.3 to 1.9 ± 0.4 cm^2, $p < 0.001$). Mean mitral pressure gradient was significantly decreased (12 ± 5 to 6 ± 2 mm Hg, $p < 0.001$).

No patient developed critical complications such as an occurrence of severe mitral regurgitation or thromboembolism. Hemodynamically insignificant left-to-right shunt (pulmonary/systemic blood flow ratio <1.3) was detected in only 4 patients (12%).

Hemodynamic changes during exercise: Exercise time was 7.4 ± 3.0 minutes before and 9.0 ± 3.2 minutes after PTMC ($p < 0.001$).

Systolic, diastolic and mean pulmonary arterial pressures decreased, and cardiac index increased after PTMC both at rest and during exercise (Table I).

Total pulmonary vascular resistance and pulmonary arteriolar resistance decreased after PTMC both at rest and during exercise (Table I).

Systolic blood pressure did not significantly change either at rest or during exercise, except in the 20 W stage. Diastolic and mean blood pressure did not change either at rest or during exercise. Systemic vascular resistance decreased both at rest and during exercise (Table I).

We subdivided all patients before PTMC into 2 groups: group with severe mitral stenosis (mitral valve area <1 cm^2, n = 9); and group with moderate stenosis (≥1 cm^2, n = 24). Mean pulmonary arterial pressure was higher and showed a more rapid increase during exercise in the severe group (Figure 1A): 33 ± 13 vs 22 ± 6 mm Hg at rest and 54 ± 14 vs 38 ± 9 mm Hg at 20 W. Total pulmonary vascular resistance was higher and displayed a more severe increase during exercise in the severe group (Figure 1B): 1,000 ± 279 vs 666 ± 349 dynes s cm^{-5}/m^2 at rest and 1,310 ± 270 vs 766 ± 469 dynes s cm^{-5}/m^2 at 20 W. Pulmonary arteriolar resistance showed a similar tendency to total pulmonary vascular resistance (Figure 1C): 279 ± 109 vs 186 ± 61 dynes s cm^{-5}/m^2 at rest and 335 ± 115 vs 207 ± 67 dynes s cm^{-5}/m^2 at 20 W. Cardiac index was lower at rest in the severe group (although not significantly), and showed a smaller increase during exercise (Figure 1D): 2.7 ± 0.5 vs 3.1 ± 0.8 liters/min/m^2 at rest and 3.4 ± 0.5 vs 4.2 ± 0.9 liters/min/m^2 at 20 W.

Moreover, all patients were subdivided after PTMC into 2 groups: group A, patients with a mitral valve area ≥1.5 cm^2 after PTMC (n = 20, except for patients with a mitral valve area ≥1.5 cm^2 before PTMC); and group B, patients with a mitral valve area <1.5 cm^2 (n = 8). Mean pulmonary arterial pressure was lower in group A than in group B during exercise (Figure 2A): 21 ± 4 vs 25 ± 7 mm Hg at rest (p = not significant [NS]), 30 ± 6 vs 40 ± 10 mm Hg at 20 W and 37 ± 5 vs 51 ± 13 mm Hg at 40 W (n = 19 vs 6). Total pulmonary vascular resistance was lower and increased more slowly during exercise in group A (Figure 2B): 510 ± 128 vs 634 ± 205 dynes s cm^{-5}/m^2 at rest (p = NS), 541 ± 150 vs 781 ± 230 dynes s cm^{-5}/m^2 at 20 W and 594 ± 180 vs 863 ± 277 dynes s cm^{-5}/m^2 at 40 W. Although pulmonary arteriolar resistance increased during exercise in group B, no increase occurred in group A (Figure 2C): 170 ± 58 vs 202 ± 61 dynes s cm^{-5}/m^2 at rest (p = NS), 162 ± 46 vs 244 ± 88 dynes s cm^{-5}/m^2 at 20 W and 163 ± 57 vs 250 ± 91 dynes s cm^{-5}/m^2 at 40 W.

DISCUSSION

Beneficial effects of PTMC include release of left atrial hypertension followed by reduction of pulmonary arterial pressure and pulmonary vascular resistance, and an increase in preload of the left ventricle leading to an increase in cardiac output.[2,7,9–18] In the patients studied, pulmonary arterial pressure and pulmonary vascular resistance decreased and cardiac index increased both at rest and during exercise after PTMC. Response of systemic blood pressure to exercise did not change and a decrease in systemic vascular resistance occurred after PTMC.

We believe that intraatrial shunt as a consequence of transseptal catheterization did not significantly affect hemodynamic results. Because, as Nobuyoshi et al[7] reported, single balloon technique creates only a small atrial septal defect which is hemodynamically insignificant.

Hemodynamics during exercise in healthy people have been reported.[19,20] With exercise, pulmonary arterial pressure and systemic blood pressure increase, and total pulmonary resistance and systemic vascular resistance decline. However, the ratio of total pulmonary resistance/systemic resistance increases with an increased work load; pulmonary arteriolar resistance remains unchanged during exercise. These findings suggest that pulmonary vasomotor control during exercise is relatively passive compared with arterioles in systemic circula-

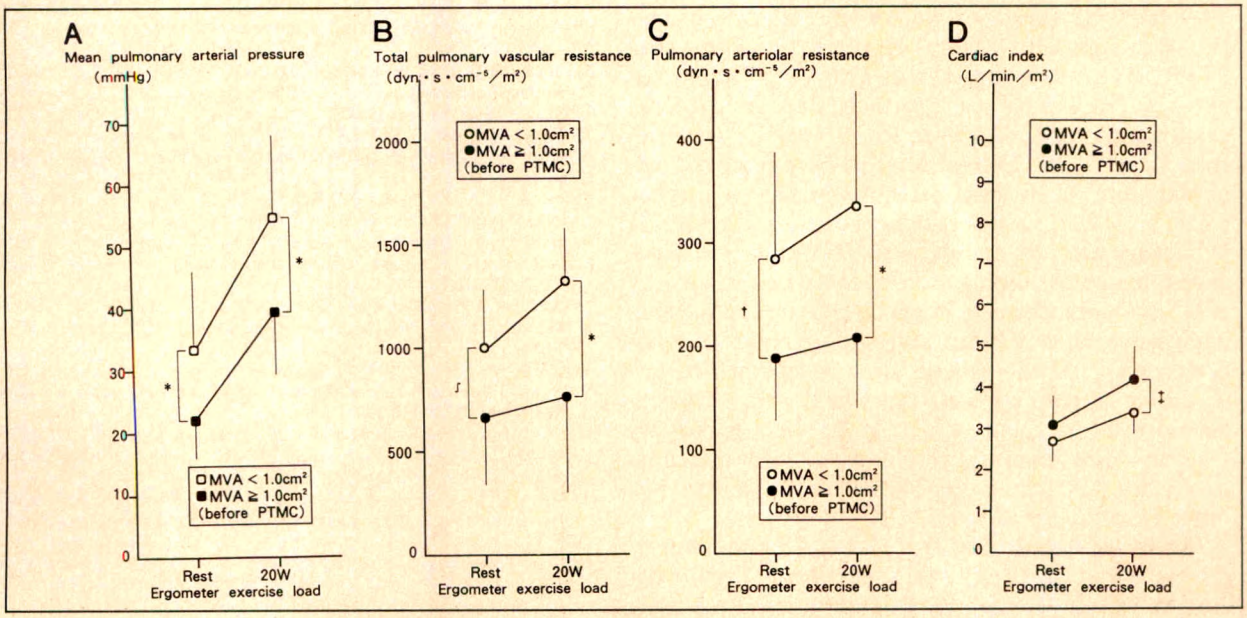


FIGURE 1. Hemodynamic data at rest and during exercise before percutaneous transvenous mitral commissurotomy (PTMC). Values are expressed as mean ± SD. MVA = mitral valve area. *p <0.001; †p <0.005; ∫p <0.01; ‡p <0.02.

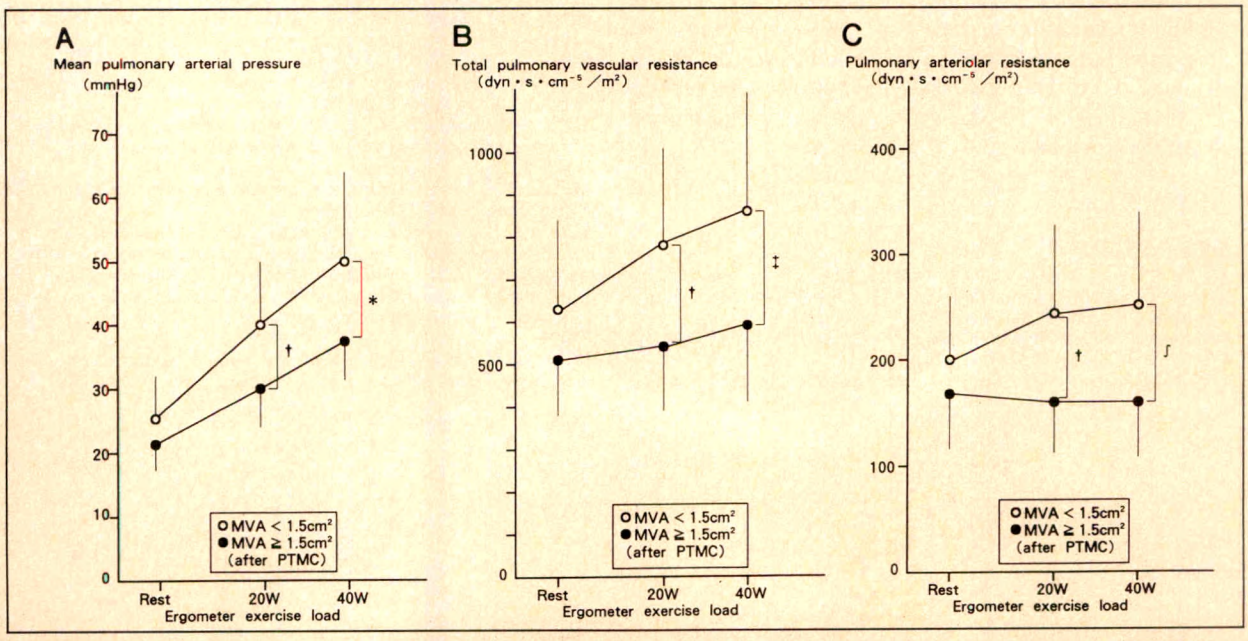


FIGURE 2. Hemodynamic data at rest and during exercise after percutaneous transvenous mitral commissurotomy (PTMC). Values are expressed as mean ± SD. MVA = mitral valve area. *p <0.001; †p <0.005; ∫p <0.01; ‡p <0.02.

tion.[19] In patients with mitral stenosis, some investigators[2,21–24] have reported that an increase in pulmonary vascular tone may occur during exercise, probably to prevent an increase in left atrial pressure. An increase in pulmonary vascular resistance is considered to cause a disproportionate increase in arterial pressure with respect to the venous pressure in the lungs and leads to an increase in right ventricular work.[23–25] Whether or not pulmonary hypertension is reversible with respect to mitral commissurotomy is considered clinically important.[24,26] In our patients, both total pulmonary vascular resistance and arteriolar resistance increased during exercise before PTMC. After PTMC, both resistances were lower. Although total pulmonary resistance still increased during exercise compared with at rest, pulmonary arteriolar resistance did not increase during exercise in patients with a mitral valve area ≥ 1.5 cm^2 after PTMC. These data suggest that high pulmonary arteriolar resistance is at least partially due to functional change and is reversible when the mitral valve area widened to ≥ 1.5 cm^2. Several workers have reported mid- or long-term follow up of patients who have undergone PTMC.[13,15,16,18] Levine et al[9] reported a decrease in pulmonary pressure and pulmonary vascular resistance at rest, but results during exercise are unknown. McKay et al[13] showed a decrease in pulmonary arterial pressure immediately after PTMC, although no progressive improvement occurred 3 months after. A long-term follow-up during exercise is necessary. A mitral valve area enlargement of ≥ 1.5 cm^2, which may prevent pulmonary vascular constriction and permits an increase in pulmonary blood flow during exercise, is believed to be a good result immediately after PTMC.

Study limitations: Because we could not obtain precise pulmonary capillary wedge pressures during exercise, we calculated pulmonary vascular resistance using the value of pulmonary diastolic pressure instead of wedge pressure. Because the absolute value of pulmonary diastolic pressure may have been higher than wedge pressure during exercise[27] in our patients, we may have have underestimated pulmonary vascular resistance. Nevertheless, we believe that our data permitted evaluation of the change in pulmonary vascular resistance before and after PTMC.

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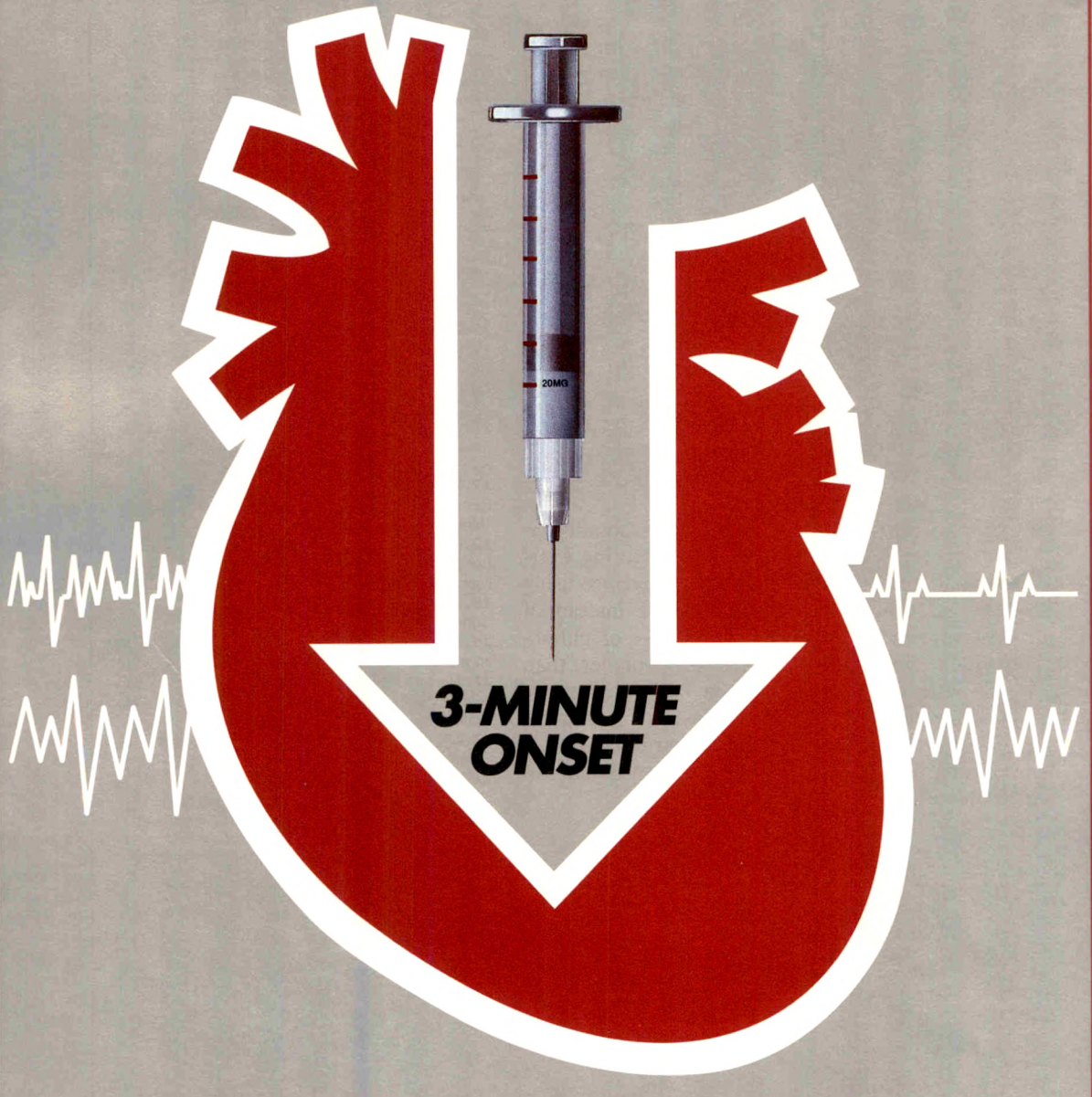
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20 mg average patient	**25 mg average patient**	

BRIEF SUMMARY

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INDICATIONS AND USAGE

CARDIZEM Injectable (diltiazem hydrochloride) is indicated for the following:

1. **Atrial Fibrillation or Atrial Flutter.** Temporary control of rapid ventricular rate in atrial fibrillation or atrial flutter. It should not be used in patients with atrial fibrillation or atrial flutter associated with an accessory bypass tract such as in Wolff-Parkinson-White (WPW) syndrome or short PR syndrome.
2. **Paroxysmal Supraventricular Tachycardia.** Rapid conversion of paroxysmal supraventricular tachycardias (PSVT) to sinus rhythm. This includes AV nodal reentrant tachycardias and reciprocating tachycardias associated with an extranodal accessory pathway such as the WPW syndrome or short PR syndrome. Unless otherwise contraindicated, appropriate vagal maneuvers should be attempted prior to administration of CARDIZEM Injectable.

The use of CARDIZEM Injectable for control of ventricular response in patients with atrial fibrillation or atrial flutter or conversion to sinus rhythm in patients with PSVT should be undertaken with caution when the patient is compromised hemodynamically or is taking other drugs that decrease any or all of the following: peripheral resistance, myocardial filling, myocardial contractility, or electrical impulse propagation in the myocardium.

For either indication and particularly when employing continuous intravenous infusion, the setting should include continuous monitoring of the ECG and frequent measurement of blood pressure. A defibrillator and emergency equipment should be readily available.

In domestic controlled trials in patients with atrial fibrillation or atrial flutter, bolus administration of CARDIZEM Injectable was effective in reducing heart rate by at least 20% in 95% of patients. CARDIZEM Injectable rarely converts atrial fibrillation or atrial flutter to normal sinus rhythm. Following administration of one or two intravenous bolus doses of CARDIZEM Injectable, response usually occurs within 3 minutes and maximal heart rate reduction generally occurs in 2 to 7 minutes. Heart rate reduction may last from 1 to 3 hours. If hypotension occurs, it is generally short-lived, but may last from 1 to 3 hours.

A 24-hour continuous infusion of CARDIZEM Injectable in the treatment of atrial fibrillation or atrial flutter maintained at least a 20% heart rate reduction during the infusion in 83% of patients. Upon discontinuation of infusion, heart rate reduction may last from 0.5 hours to more than 10 hours (median duration 7 hours). Hypotension, if it occurs, may be similarly persistent.

In the controlled clinical trials, 3.2% of patients required some form of intervention (typically, use of intravenous fluids or the Trendelenburg position) for blood pressure support following CARDIZEM Injectable.

In domestic controlled trials, bolus administration of CARDIZEM Injectable was effective in converting PSVT to normal sinus rhythm in 88% of patients within 3 minutes of the first or second bolus dose.

Symptoms associated with the arrhythmia were improved in conjunction with decreased heart rate or conversion to normal sinus rhythm following administration of CARDIZEM Injectable.

CONTRAINDICATIONS

CARDIZEM Injectable is contraindicated in:

1. Patients with sick sinus syndrome except in the presence of a functioning ventricular pacemaker.
2. Patients with second- or third-degree AV block except in the presence of a functioning ventricular pacemaker.
3. Patients with severe hypotension or cardiogenic shock.
4. Patients who have demonstrated hypersensitivity to the drug.
5. Intravenous diltiazem and intravenous beta-blockers should not be administered together or in close proximity (within a few hours).
6. Patients with atrial fibrillation or atrial flutter associated with an accessory bypass tract such as in WPW syndrome or short PR syndrome.

   As with other agents which slow AV nodal conduction and do not prolong the refractoriness of the accessory pathway (eg, verapamil, digoxin), in rare instances patients in atrial fibrillation or atrial flutter associated with an accessory bypass tract may experience a potentially life-threatening increase in heart rate accompanied by hypotension when treated with CARDIZEM Injectable. As such, the initial use of CARDIZEM Injectable should be, if possible, in a setting where monitoring and resuscitation capabilities, including DC cardioversion/defibrillation, are present (see OVERDOSAGE). Once familiarity of the patient's response is established, use in an office setting may be acceptable.
7. Patients with ventricular tachycardia. Administration of other calcium channel blockers to patients with wide complex tachycardia (QRS ≥ 0.12 seconds) has resulted in hemodynamic deterioration and ventricular fibrillation. It is important that an accurate pretreatment diagnosis distinguish wide complex QRS tachycardia of supraventricular origin from that of ventricular origin prior to administration of CARDIZEM Injectable.

WARNINGS

1. **Cardiac Conduction.** Diltiazem prolongs AV nodal conduction and refractoriness that may rarely result in second- or third-degree AV block in sinus rhythm. Concomitant use of diltiazem with agents known to affect cardiac conduction may result in additive effects (see Drug Interactions). If high-degree AV block occurs in sinus rhythm, intravenous diltiazem should be discontinued and appropriate supportive measures instituted (see OVERDOSAGE).
2. **Congestive Heart Failure.** Although diltiazem has a negative inotropic effect in isolated animal tissue preparations, hemodynamic studies in humans with normal ventricular function and in patients with a compromised myocardium, such as severe CHF, acute MI, and hypertrophic cardiomyopathy, have not shown a reduction in cardiac index nor consistent negative effects on contractility (dp/dt). Administration of oral diltiazem in patients with acute myocardial infarction and pulmonary congestion documented by x-ray on admission is contraindicated. Experience with the use of CARDIZEM Injectable in patients with impaired ventricular function is limited. Caution should be exercised when using the drug in such patients.
3. **Hypotension.** Decreases in blood pressure associated with CARDIZEM Injectable therapy may occasionally result in symptomatic hypotension (3.2%). The use of intravenous diltiazem for control of ventricular response in patients with supraventricular arrhythmias should be undertaken with caution when the patient is compromised hemodynamically. In addition, caution should be used in patients taking other drugs that decrease peripheral resistance, intravascular volume, myocardial contractility or conduction.
4. **Acute Hepatic Injury.** In rare instances, significant elevations in enzymes such as alkaline phosphatase, LDH, SGOT, SGPT, and other phenomena consistent with acute hepatic injury have been noted following oral diltiazem. Therefore, the potential for acute hepatic injury exists following administration of intravenous diltiazem.
5. **Ventricular Premature Beats (VPBs).** VPBs may be present on conversion of PSVT to sinus rhythm with CARDIZEM Injectable. These VPBs are transient, are typically considered to be benign, and appear to have no clinical significance. Similar ventricular complexes have been noted during cardioversion, other pharmacologic therapy, and during spontaneous conversion of PSVT to sinus rhythm.

PRECAUTIONS

General. CARDIZEM (diltiazem hydrochloride) is extensively metabolized by the liver and excreted by the kidneys and in bile. The drug should be used with caution in patients with impaired renal or hepatic function (see WARNINGS). High intravenous dosages (4.5 mg/kg tid) administered to dogs resulted in significant bradycardia and alterations in AV conduction. In subacute and chronic dog and rat studies designed to produce toxicity, high oral doses of diltiazem were associated with hepatic damage. In special subacute hepatic studies, oral doses of 125 mg/kg and higher in rats were associated with histological changes in the liver, which were reversible when the drug was discontinued. In dogs, oral doses of 20 mg/kg were also associated with hepatic changes; however, these changes were reversible with continued dosing.

Dermatologic events progressing to erythema multiforme and/or exfoliative dermatitis have been infrequently reported following oral diltiazem. Therefore, the potential for these dermatologic reactions exists following exposure to intravenous diltiazem. Should a dermatologic reaction persist, the drug should be discontinued.

Drug Interactions. Due to potential for additive effects, caution is warranted in patients receiving CARDIZEM Injectable concomitantly with any agent(s) known to affect cardiac contractility and/or SA or AV node conduction (see WARNINGS).

As with all drugs, care should be exercised when treating patients with multiple medications. CARDIZEM undergoes extensive metabolism by the cytochrome P-450 mixed function oxidase system. Although specific pharmacokinetic drug-drug interaction studies have not been conducted with single intravenous injection or constant rate intravenous infusion, coadministration of CARDIZEM Injectable with other agents which primarily undergo the same route of biotransformation may result in competitive inhibition of metabolism.

Digitalis: Intravenous diltiazem has been administered to patients receiving either intravenous or oral digitalis therapy. The combination of the two drugs was well tolerated without serious adverse effects. However, since both drugs affect AV nodal conduction, patients should be monitored for excessive slowing of the heart rate and/or AV block.

Beta-blockers: Intravenous diltiazem has been administered to patients on chronic oral beta-blocker therapy. The combination of the two drugs was generally well tolerated without serious adverse effects. If intravenous diltiazem is administered to patients receiving chronic oral beta-blocker therapy, the possibility for bradycardia, AV block, and/or depression of contractility should be considered (see CONTRAINDICATIONS). ***Oral*** administration of diltiazem with propranolol in five normal volunteers resulted in increased propranolol levels in all subjects and bioavailability of propranolol was increased approximately 50%. In vitro, propranolol appears to be displaced from its binding sites by diltiazem.

Anesthetics: The depression of cardiac contractility, conductivity, and automaticity as well as the vascular dilation associated with anesthetics may be potentiated by calcium channel blockers. When used concomitantly, anesthetics and calcium blockers should be titrated carefully.

Carcinogenesis, Mutagenesis, Impairment of Fertility. A 24-month study in rats at oral dosage levels of up to 100 mg/kg/day, and a 21-month study in mice at oral dosage levels of up to 30 mg/kg/day showed no evidence of carcinogenicity. There was also no mutagenic response in vitro or in vivo in mammalian cell assays or in vitro in bacteria. No evidence of impaired fertility was observed in a study performed in male and female rats at oral dosages of up to 100 mg/kg/day.

Pregnancy. Category C. Reproduction studies have been conducted in mice, rats, and rabbits. Administration of oral doses ranging from five to ten times greater (on a mg/kg basis) than the daily recommended oral antianginal therapeutic dose has resulted in embryo and fetal lethality. These doses, in some studies, have been reported to cause skeletal abnormalities. In the perinatal postnatal studies there was some reduction in early individual pup weights and survival rates. There was an increased incidence of stillbirths at doses of 20 times the human oral antianginal dose or greater.

There are no well-controlled studies in pregnant women; therefore, use CARDIZEM in pregnant women only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers. Diltiazem is excreted in human milk. One report with oral diltiazem suggests that concentrations in breast milk may approximate serum levels. If use of CARDIZEM is deemed essential, an alternative method of infant feeding should be instituted.

Pediatric Use. Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

The following adverse reaction rates are based on the use of CARDIZEM Injectable in over 400 domestic clinical trial patients with atrial fibrillation/flutter or PSVT under double-blind or open-label conditions. Worldwide experience in over 1,300 patients was similar.

Adverse events reported in controlled and uncontrolled clinical trials were generally mild and transient. Hypotension was the most commonly reported adverse event during clinical trials. Asymptomatic hypotension occurred in 4.3% of patients. Symptomatic hypotension occurred in 3.2% of patients. When treatment for hypotension was required, it generally consisted of administration of saline or placing the patient in the Trendelenburg position. Other events reported in at least 1% of the diltiazem-treated patients were injection site reactions (eg, itching, burning)—3.9%, vasodilation (flushing)—1.7%, and arrhythmia (junctional rhythm or isorhythmic dissociation)—1.0%.

In addition, the following events were reported infrequently (less than 1%):

Cardiovascular:	Atrial flutter, AV block first degree, AV block second degree, bradycardia, chest pain, congestive heart failure, sinus pause, sinus node dysfunction, syncope, ventricular arrhythmia, ventricular fibrillation, ventricular tachycardia.
Dermatologic:	Pruritus, sweating.
Gastrointestinal:	Constipation, elevated SGOT or alkaline phosphatase, nausea, vomiting.
Nervous System:	Dizziness, paresthesia.
Other:	Amblyopia, asthenia, dry mouth, dyspnea, edema, headache, hyperuricemia.

Although not observed in clinical trials with CARDIZEM Injectable, other reactions associated with oral diltiazem may occur.

Product information as of October 1991

References: 1. Cardizem Injectable prescribing information. 2. Ellenbogen KA, Dias VC, Plumb VJ, Heywood JT, Mirvis DM. *J Am Coll Cardiol.* 1991;18:891-897.

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CARDIZEM INJECTABLE...HEART RATE CONTROL THAT IS FAST, SAFE, AND CONTINUOUS

Comparison of the Cardiotoxicity of Ethanol in Women Versus Men

Markku Kupari, MD, and Pekka Koskinen, MD

Subclinical left ventricular (LV) dysfunction is a common occurrence in alcoholic men but has been claimed to be absent or very rare in alcoholic women. M-mode echocardiography was performed to study LV size, mass and systolic function, and Doppler ultrasound to study LV filling in 14 chronic female alcoholics aged 24 to 48 years and in 2 age-matched control groups consisting of 17 healthy women and 22 alcoholic men. Compared with healthy women, female alcoholics had no differences in heart rate or blood pressure but a shorter LV end-diastolic diameter (mean ± standard deviation, 46 ± 4 vs 48 ± 3 mm, p <0.05), lower fractional shortening (31 ± 6 vs 34 ± 3%, p <0.05), increased wall thickness to radius ratio (0.43 ± 0.08 vs 0.37 ± 0.05, p <0.05), reduced peak early diastolic transmitral velocity (45 ± 11 vs 68 ± 7 cm/s, p <0.001), reduced deceleration of the early diastolic velocity (−274 ± 69 vs −572 ± 107 cm/s², p <0.001), and an increased atrial filling fraction (35 ± 12 vs 27 ± 5%, p <0.05). Although alcoholic men had a longer duration of heavy drinking than alcoholic women (median 19 vs 5 years, p <0.001), and a higher systolic blood pressure (140 ± 17 vs 120 ± 17 mm Hg, p <0.001), there were no statistically significant differences between the sexes either in LV diameters, wall thickness or mass normalized to body area, or in indexes of systolic or diastolic LV function. It is concluded that subclinical LV dysfunction is also a common occurrence in alcoholic women. Contrary to earlier beliefs, the cardiotoxicity of ethanol does not spare the female heart.

(Am J Cardiol 1992;70:645–649)

The adverse effects of chronic alcohol abuse on the heart include development of subclinical left ventricular (LV) hypertrophy and dysfunction.[1–5] Their exact pathogenesis is still poorly known, but the severity of eventual cardiac injury is likely to depend also on genetic, metabolic or environmental factors modifying the effects of alcohol.[1,6,7] Women have a higher bioavailability of alcohol than men because of less gastric oxidation,[8] and they are generally considered more vulnerable to the organ toxicity of alcohol abuse.[9,10] With regard to heart muscle involvement, the influence of gender is not well known, since the overwhelming majority of previous studies have included either purely or predominantly male alcoholics. In fact, only 1 study[11] has systematically compared the cardiac effects of long-term alcohol abuse between men and women. In that study, subclinical impairment of systolic time intervals was evident in male but not in female alcoholics, which was considered to indicate resistance of the female myocardium to the injurious effects of ethanol. However, these data[11] do not establish a difference between the sexes with regard to myocardial involvement, because differences in systolic time intervals were interpreted without any knowledge of LV size, mass or loading conditions except for arterial blood pressure. To assess whether the female heart really tolerates alcohol abuse without structural or functional deterioration, we studied a group of asymptomatic alcoholic women using combined 2-dimensional, M-mode and Doppler echocardiography. The present report contains data on LV size, mass, and systolic as well as diastolic function and compares female alcoholics with healthy women and with alcoholic men.

METHODS

Female alcoholics: Sixteen consecutive female alcoholics were evaluated during their hospitalization for detoxification and research purposes. For inclusion into our study, they had to be free of signs and symptoms of any cardiovascular, metabolic or respiratory disease as assessed by history, physical examination, a 12-lead electrocardiogram and routine laboratory tests. Furthermore, either an M-mode ultrasound study of LV function or a Doppler interrogation of mitral inflow had to be technically possible. One patient was excluded because of liver cirrhosis and another because of heavy drug abuse. The final study group consisted of 14 women aged 24 to 48 years (mean 38). Their height and weight (mean ± standard deviation) were 165 ± 5 cm and 64 ± 11 kg, respectively. The calculated body surface area averaged 1.68 ± 0.14 m^2. Two women had amenorrhea and 11 had normal menstruation; these data were missing in 1 subject. Ten persons were daily smokers.

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Control groups (healthy women and alcoholic men): For a nonalcoholic control group, we studied 17 female volunteers aged 34 to 45 years (mean 37). They were healthy on the basis of history, clinical examination, a 12-lead electrocardiogram and routine laboratory assessment. Their self-reported habitual ethanol consumption was <10 g/day. Their height and weight averaged 165 ± 8 cm and 64 ± 9 kg, respectively. The calculated body surface area was 1.68 ± 0.13 m^2. All had regular menstrual cycles and no woman was engaged in competitive sports. Six women were daily smokers.

For another control group, we evaluated 25 alcoholic men hospitalized for detoxification and research purposes. Their inclusion criteria were identical to those of the female alcoholics (see before). One man was excluded because of previously diagnosed coronary artery disease, and neither M-mode echocardiography nor Doppler ultrasound were technically successful in 2 persons. The control group consisted of the remaining 22 alcoholic men who were aged 23 to 50 years (mean 42, p >0.10 compared with alcoholic women). All except 4 men were regular smokers. Their height and weight were 177 ± 8 cm and 76 ± 12 kg, respectively. The body surface area was calculated as 1.93 ± 0.18 m^2.

Protocol: All study subjects underwent routine laboratory testing including measurement of mean red cell corpuscular volume (Coulter autoanalyzer, reference range 80 to 96 fl) and enzymatic determination of aspartate aminotransferase (reference range <40 U/liter) and γ-glutamyltransferase (reference range <46 U/liter for men and <30 U/liter for women). A 12-lead electrocardiogram was obtained routinely but chest x-rays were recorded only when clinically indicated. The alcoholics were carefully questioned regarding the total duration of heavy drinking, the length of the last uninterrupted drinking period and the types and amounts of drinks typically consumed in 1 day. The drinks were converted to grams of absolute ethanol and added up to give an estimate of daily consumption. The echocardiographic study was scheduled on the third to fifth day after admission. If the subject still had symptoms of alcohol withdrawal at that time, the examination was postponed until obvious withdrawal symptoms were over. Blood pressure was measured by the cuff method at the time of the ultrasound study. All cardiovascular examinations were performed ≥2 hours after the last meal. The healthy women were studied as outpatients. The protocol was approved by the institutional ethics committee, and each subject gave a verbal informed consent.

Imaging echocardiography: LV imaging studies were performed with cross-sectional scanners (Toshiba SSH-60A, Toshiba SSH-160A, Aloka SSD-830) equipped with 2.5 and 3.7 MHz phased-array transducers and a strip-chart recorder. A 2-dimensional evaluation was made first to rule out segmental abnormalities of LV function. A standard M-mode LV study was performed thereafter by methods previously described in detail[12]; the recording speed was 50 mm/s. High-quality studies were obtained in 12 of 14 alcoholic women, 17 of 17 healthy women and in 16 of 22 alcoholic men. The strips were coded and later measured blindly using an x–y digitizer and computer assistance. In a few subjects, frozen M-mode images were analyzed instead of strip-chart recordings. The following LV parameters were measured as recently described[13]: end-diastolic diameter, end-systolic diameter, fractional shortening, interventricular septal thickness, posterior wall thickness, radius to thickness ratio, and mass. LV diameters, wall thicknesses and mass were also adjusted to body size by dividing with body surface area. All measurements were averaged over 3 to 5 cardiac cycles. The reproducibility of our LV studies has been validated and reported previously.[12]

Doppler echocardiography: Pulsed Doppler recordings of transmitral flow were performed with the Doppler units of the echocardiographs previously specified, and using 2.5 MHz transducers. The studies were performed from an apical transducer position with the subject in left lateral recumbency. The ultrasound beam was directed parallel to the assumed LV inflow and the 3 to 5 mm sample volume was placed between the bases of the mitral valve leaflets at or just distal to the mitral annulus. The position of the sample volume was then adjusted, with the help of audible and visible Doppler signals or color Doppler visualization of mitral inflow, to obtain maximal and sharply defined velocity wave forms. The velocity spectra were recorded during quiet respiration together with an electrocardiogram and an external phonocardiogram at a paper speed of 50 or 100 mm/s. High-quality tracings were obtained in 13 of 14 alcoholic women, 16 of 17 healthy women and 19 of 22 alcoholic men. The recordings were coded and analyzed blindly. The midpoints of the darkest portions of the velocity wave forms were traced on the digitizing table to obtain the following measurements, as described in detail elsewhere[14,15]: the peak early diastolic velocity, the peak late diastolic (atrial) velocity with the early to atrial peak velocity ratio, the relaxation time, the acceleration of early flow velocity, the deceleration of early flow velocity, and the atrial filling fraction. All Doppler measurements were averaged over 5 cardiac cycles. The reproducibility of our Doppler measurements has been confirmed and reported earlier.[14]

Statistical analysis: Student's nonpaired *t* test was used to compare the female alcoholics separately with the 2 groups of control subjects. If the distribution of the data was grossly abnormal, the Mann-Whitney U test was performed. The results are given as mean ± standard deviation or, if more appropriate, as median and range. A p value <0.05 was considered statistically significant.

RESULTS

Drinking histories and biochemical markers of alcohol abuse: Most of the female alcoholics and their male alcoholic controls were episodic drinkers. Their drinking histories are summarized in Table I, which also includes data on biochemical markers of alcohol abuse in the 3 study groups. Alcoholic women had a shorter duration of heavy drinking than alcoholic men, but otherwise the drinking history and the laboratory test results were not significantly different. The biochemical markers of alcohol abuse were clearly higher in the alcoholic than in

TABLE I Drinking Histories and Biochemical Markers of Alcohol Abuse in Female Alcoholics, Healthy Women and Alcoholic Men

	Alcoholic Women (n = 14)		Healthy Women (n = 17)		Alcoholic Men (n = 22)	
	Median	Range	Median	Range	Median	Range
Duration of heavy drinking (years)	5	0.5–25	—	—	19	5–30†
Length of the last drinking period (wk)	6	1–200	—	—	6	0.5–78
Daily ethanol consumption (g)	200	70–575	—	—	230	80–600
Mean red cell corpuscular volume (fl)	93	88–102	90	83–96*	96	86–115
Aspartate aminotransferase (U/liter)	74	19–369	18	12–30†	78	19–293
γ-glutamyltransferase (U/liter)	110	15–1121	14	6–28†	120	24–1510

*$p < 0.05$; †$p < 0.001$ compared with alcoholic women (Mann-Whitney U test).

TABLE II Heart Rate, Blood Pressure and Echocardiographic Left Ventricular Measurements in Alcoholic and Healthy Women, and in Alcoholic Men

Measurement	Alcoholic Women (n = 14*)	Healthy Women (n = 17)	Alcoholic Men (n = 22*)
Heart rate (beats/min)	76 ± 11	72 ± 9	77 ± 14
Systolic blood pressure (mm Hg)	120 ± 17	123 ± 11	140 ± 17‡
Diastolic blood pressure (mm Hg)	85 ± 15	79 ± 7	92 ± 13
Left ventricular			
end-diastolic diameter (mm)	46 ± 4	48 ± 3†	48 ± 5
end-systolic diameter (mm)	32 ± 4	32 ± 3	35 ± 5
fractional shortening (%)	31 ± 6	34 ± 3†	28 ± 7
interventricular septal thickness (mm)	10 ± 2	8 ± 1†	11 ± 2†
posterior wall thickness (mm)	10 ± 1	9 ± 1	11 ± 1‡
thickness to radius ratio	0.43 ± 0.08	0.37 ± 0.05†	0.48 ± 0.09
mass (g)	126 ± 19	120 ± 22	163 ± 28§

*Echocardiographic measurements were obtained in 12 alcoholic women and 16 alcoholic men.
†$p < 0.05$; ‡$p < 0.01$; §$p < 0.001$ compared with alcoholic women (Student's *t* test).
Data are mean ± standard deviation.

TABLE III Doppler Indexes of Left Ventricular Filling in Alcoholic and Healthy Women, and in Alcoholic Men

Doppler Index	Alcoholic Women (n = 14*)	Healthy Women (n = 17*)	Alcoholic Men (n = 22*)
Peak early diastolic velocity (cm/s)	45 ± 11	68 ± 7§	47 ± 12
Peak atrial velocity (cm/s)	40 ± 10	44 ± 7	45 ± 10
Early to atrial peak velocity ratio	1.22 ± 0.59	1.54 ± 0.25	1.09 ± 0.44
Relaxation time (ms)	178 ± 13	172 ± 18	178 ± 27
Acceleration of early flow velocity (cm/s^2)	476 ± 119	712 ± 194‡	548 ± 220
Deceleration of early flow velocity (cm/s^2)	−274 ± 69	−572 ± 107§	−292 ± 143
Atrial filling fraction (%)	35 ± 12	27 ± 5†	38 ± 13

*Doppler measurements were obtained in 13 alcoholic women, 16 healthy women and 19 alcoholic men.
*$p < 0.05$; ‡$p < 0.01$; §$p < 0.001$ compared with alcoholic women (Student's *t* test).
Data are mean ± standard deviation.

the healthy women; no nonalcoholic individual had any elevated value.

Cardiovascular measurements in alcoholic versus healthy women (Tables II and III): Table II shows that there were no statistically significant differences in heart rate or blood pressure between the alcoholic and healthy women. The alcoholics had a significantly smaller LV end-diastolic diameter and a higher septal thickness, resulting in increased thickness to radius ratio. There was no statistically significant difference in the LV mass, but fractional shortening was lower in the alcoholics, indicating impairment of systolic LV function.

Table III shows that the alcoholics had slower acceleration, smaller peak value and slower deceleration of the early diastolic transmitral velocity, accompanied by increased atrial filling fraction. Although the difference in the peak velocity ratio (see Table III) was not quite statistically significant ($p = 0.06$), the diastolic indexes indicate impaired LV filling in the alcoholic women. Figure 1 demonstrates typical differences in the transmitral diastolic velocity tracings of alcoholic and healthy women.

Cardiovascular measurements in female versus male alcoholics: ALL ALCOHOLICS: Tables II and III also compare the cardiovascular measurements between the 2 alcoholic groups. Alcoholic men had a higher systolic blood pressure and higher LV wall thicknesses and mass, but no other differences between the sexes were found. Furthermore, when adjusted to body area, LV

wall thickness and mass measurements were not statistically significantly different. Septal thickness index averaged 5.7 ± 1.2 mm/m^2 in women vs 5.9 ± 1.1 mm/m^2 in men ($p = 0.61$), posterior wall thickness index was 5.9 ± 1.2 mm/m^2 in women vs 6.0 ± 0.8 mm/m^2 in men ($p = 0.74$), and LV mass index was 76 ± 14 g/m^2 in women vs 85 ± 14 g/m^2 in men ($p = 0.09$).

ALCOHOLICS WITH BLOOD PRESSURE ≤150/95 mm Hg: Although none of the alcoholics in this study had known hypertension, several — the men in particular — had high blood pressure readings at the time of our study. Therefore we also compared cardiovascular measurements between female and male alcoholics having a systolic blood pressure ≤150 mm Hg and a diastolic blood pressure ≤95 mm Hg. Eleven women and 14 men filled this criterion. Both the M-mode and Doppler ultrasound data were available for analysis in 11 female and 12 male alcoholics. There were no statistically significant differences between the sexes in fractional shortening (31 ± 6% in women vs 28 ± 7% in men, $p = 0.21$) or in any of the LV filling indexes. LV diameters, posterior wall thickness and mass were higher in men, but again, after normalization to body area, no statistically significant differences remained. LV mass index averaged 76 ± 14 g/m^2 in alcoholic women and 83 ± 14 g/m^2 in alcoholic men ($p = 0.18$).

DISCUSSION

The message of our data is that the female heart is not resistant to the toxic effects of alcohol abuse. Alcoholic women had both systolic and diastolic LV impairment compared with age-matched healthy women, and there were no statistically significant differences in LV anatomy or function between alcoholic men and women, except for those related to body size. The lack of differences between the sexes is even more significant because men had a longer duration of alcoholism and a higher systolic blood pressure at the time of our study. The trend toward a higher LV mass index in the male alcoholics was expected since, even in healthy populations, men have higher LV mass normalized to body area.[16]

These comparisons between alcoholic and healthy women gave essentially similar results as our earlier study in men,[17] except that an increase in LV mass was not observed. The relatively short duration of heavy drinking in alcoholic women may be of importance in this respect, although it is still unsettled whether and how the subclinical heart muscle involvement depends on the length and severity of alcoholism.[18,19] Alterations in LV filling indexes in alcoholic women were at least as prominent as reduction in systolic function. Combined with increased atrial contribution to LV filling, abnormalities of early diastolic velocity with delayed acceleration and deceleration are compatible with an impairment in LV relaxation.[20] A primary diastolic abnormality could also explain the reduced LV end-diastolic size (preload), which in turn could have contributed to the systolic impairment.

In their study, Wu et al[11] examined 14 alcoholic and 11 nonalcoholic women, and they found no differences in systolic time intervals. Since alcoholic men who were studied simultaneously had impaired systolic time intervals, and because there was also a direct male-female difference, the data were interpreted as suggesting a role for sex hormones in the development of preclinical alcoholic cardiomyopathy.[11] Alcoholic women in that study differed from our patients in that they had a longer duration of heavy drinking (mean 14 years) and a very high prevalence of liver cirrhosis (10 of 14). The latter fact may be of particular importance since the female control group did not include subjects with nonalcoholic cirrhosis. Some alcoholics with cirrhosis have reduced peripheral vascular resistance and a high cardiac output,[21,22] which could mask the effects of alcohol abuse on the heart muscle. Without any other knowledge of LV size, wall thickness and function, a lack of difference in the systolic time intervals between alcohol-

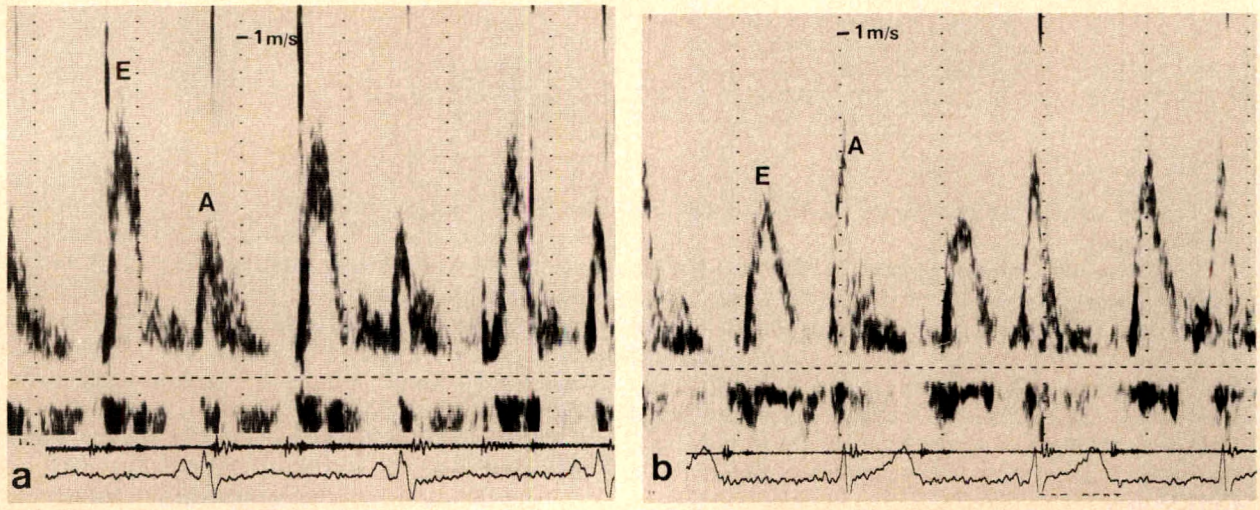


FIGURE 1. Transmitral flow velocity recordings in a 45-year-old healthy nonalcoholic woman *(A)* and in a 48-year-old alcoholic woman who had drunk heavily for 25 years *(B)*. Note the differences in the peak early (E) and late (A) diastolic velocities. The E/A ratio and the atrial filling fraction measured 1.68 and 22%, respectively, in the healthy woman, compared with 0.88 and 37% in the alcoholic. The velocity waveform in the alcoholic woman *(B)* is suggestive of impaired left ventricular relaxation. Heart rate during the study was similar in both subjects (62 to 65 beats/min).

ic and nonalcoholic women cannot be considered definitive evidence of a lack of myocardial involvement. We therefore believe that differences in the study population and in the technique of LV measurements best explain the conflict between the data reported by Wu et al[11] and by us. We also believe that, although the female sex hormones undoubtedly can influence heart muscle,[23] a full protection against the toxicity of ethanol abuse would be very difficult to explain biochemically.

A difference between men and women has previously been reported also with regard to the acute cardiac effects of alcohol. Timmis et al[24] found an impairment in systolic time intervals in men, but not in women, ingesting a varying dose of ethanol. The study was uncontrolled and retrospectively analyzed, however, and the systolic time intervals were measured only once after ethanol intake. Another study, which combined echocardiographic LV measurements with systolic time intervals and included a control experiment with juice, found no difference between the acute cardiac effects of ethanol in healthy men and women.[25]

The mechanisms and development of clinically evident dilated alcoholic cardiomyopathy are still poorly understood. Studies in adult animals have uniformly failed to produce dilated LV failure by chronic ethanol administration,[7,26] and only a minority of human alcoholics ever develop severe cardiomyopathy despite the high prevalence of subclinical LV involvement.[27] It thus appears likely that either individual sensitivity or factors potentiating or modifying the myocardial toxicity of ethanol contribute to the development of severe cardiomyopathy. Because dilated congestive cardiomyopathy appears to occur more often in male than female alcoholics, gender has been considered a possible modifying factor. According to our data, a difference between men and women in myocardial toxicity of ethanol is very unlikely. Other mechanisms — such as differences between men and women in factors aggravating alcoholic injury — should be sought in order to explain the predilection of men to develop severe cardiomyopathy.

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Altered Cardiac Hemodynamic and Electrical State in Normal Sinus Rhythm After Chronic Dual-Chamber Pacing for Relief of Left Ventricular Outflow Obstruction in Hypertrophic Cardiomyopathy

Dorothea McAreavey, MD, and Lameh Fananapazir, MD

Dual-chamber (DDD) pacing relieves left ventricular (LV) outflow tract obstruction in patients with hypertrophic cardiomyopathy. The reduction in LV outflow gradient persists in some patients after cessation of pacing. Twelve-lead and signal-averaged electrocardiograms were obtained before and after 12 weeks of DDD pacing in 18 patients with obstructive hypertrophic cardiomyopathy to determine whether the altered hemodynamic state after chronic pacing is accompanied by electrical changes. Hemodynamic studies were performed at baseline and at follow-up. Signal-averaged electrocardiograms were obtained using a Corazonix Predictor and bidirectional filters at 25 Hz to a noise level of <0.5 μV. At follow-up, LV outflow tract gradients were reduced significantly during DDD pacing and with cessation of pacing in sinus rhythm by 56 ± 10 and 47 ± 10 mm Hg, respectively ($p < 0.001$). There was no simple relation between changes in LV outflow tract gradient and in the electrocardiogram. For example, amplitude of the R wave in $V_{5,6}$ was reduced by ≥0.5 mv in 4 patients, unchanged in 12 and increased in 2. Similarly, the S wave in leads $V_{1,2}$ was reduced in 7 patients, unchanged in 7 and increased in 4. The T wave became more negative (≥0.1 mv) in leads II, III, aVF and $V_{5,6}$ in 13 patients and more positive in leads I and aVL in 12. The QRS was also altered by signal-averaged electrocardiographic criteria; duration of the total QRS and root-mean-square voltage of the QRS of the filtered Y axis increased (106 ± 12 to 112 ± 13 ms [$p = 0.036$] and 170 ± 82 to 195 ± 102 μV [$p = 0.059$], respectively).

In conclusion, chronic DDD pacing significantly reduces obstruction to LV outflow, and after discontinuation of chronic DDD pacing, there is evidence of altered mechanical as well as electrical myocardial state.

(Am J Cardiol 1992;70:651–656)

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Recent studies suggested that dual-chamber (DDD) pacing in patients with hypertrophic cardiomyopathy (HC) who are refractory to medical treatment results in clinical and hemodynamic improvement.[1,2] The reduction in left ventricular (LV) outflow tract gradient persists after temporary discontinuation of chronic pacing in most patients,[1] but the mechanism of this altered hemodynamic state is uncertain. In normal subjects, right ventricular pacing gradually changes repolarization, a phenomenon termed "electrotonic modulation" of the T wave.[3] This effect is observed after 48 hours of cardiac pacing, but may persist for up to 40 days. The present investigation examines whether DDD pacing in obstructive HC resulted in alterations in depolarization and repolarization phases of cardiac electrical activation of the heart, and examines the relation of cardiac electrical changes to alterations in LV hemodynamic state.

METHODS

The study cohort comprised 18 patients (10 women and 8 men, mean age 48 ± 14 years) with obstructive HC (LV outflow tract gradient >30 mm Hg at rest or >50 mm Hg with provocation) investigated between May 1990 and October 1991, because of symptoms refractory to drug therapy with verapamil (≥80 mg, 3 times daily) and propranolol (≥80 mg, 4 times daily) or atenolol (100 mg/day). All patients were in New York Heart Association functional class III or IV. Symptoms included dyspnea on exertion and at rest (n = 15), palpitations (n = 13), chest pain (n = 17) and syncope (n = 7). Ventricular tachycardia had not been documented in any case (negative Holter/electrophysiologic study). No patient had a previous cardiac arrest. DDD pacemakers were implanted to relieve LV outflow tract obstruction, as an alternative treatment to cardiac surgery. Informed consent was obtained in accordance with a study protocol approved by the institute review board of the National Heart, Lung, and Blood Institute. The diagnosis of HC was obtained by the echocardiographic appearances of a nondilated hypertrophied left ventricle in the absence of systemic hypertension or other cardiac or systemic cause for LV hypertrophy.[4] Drug treatment was discontinued 5 half-lives before investigations that included 12-lead and signal-averaged electrocardiograms in normal sinus rhythm, echocardiography, and right- and left-sided heart catheterization before and 12 weeks after insertion of a DDD pacemaker. All patients

TABLE I Clinical Features of Patients with Hypertrophic Cardiomyopathy Undergoing Chronic Dual-Chamber (DDD) Pacing

	Baseline	Follow-Up (12 weeks) DDD Pacing	Follow-Up (12 weeks) Sinus Rhythm
Echocardiographic dimensions (mm)			
Septum	23 ± 5		24 ± 5
LV free wall	12 ± 5		13 ± 6
LV diastolic dimension	43 ± 5		41 ± 5
LV systolic dimension	27 ± 5		23 ± 4*
Left atrium	47 ± 7		46 ± 5
Aortic root	31 ± 3		31 ± 4
Hemodynamic data (mm Hg)			
Right atrium	6 ± 3	5 ± 2	7 ± 3
Right ventricle, systolic	36 ± 14	33 ± 13	37 ± 14
Pulmonary artery, systolic	36 ± 15	32 ± 11	34 ± 15
Pulmonary artery, diastolic	17 ± 8	17 ± 8	19 ± 12
Pulmonary artery, mean	23 ± 12	21 ± 9	21 ± 8
Pulmonary capillary wedge	14 ± 6	12 ± 5	15 ± 9
Cardiac output (L/min)	4.9 ± 1.0	5.5 ± 1.4	5.0 ± 1.1
Cardiac index (L/min/m^2)	2.6 ± 0.5	2.8 ± 0.6	2.8 ± 0.5
LV systolic	210 ± 43	165 ± 58†	177 ± 56*
LV diastolic	23 ± 8	—	19 ± 6
Aortic systolic	114 ± 32	127 ± 28	128 ± 33
Aortic diastolic	67 ± 16	72 ± 15	72 ± 16
Aortic mean	88 ± 18	93 ± 18	95 ± 22
LV outflow gradient	94 ± 47	39 ± 51†	49 ± 45†

*$p < 0.01$; †$p < 0.001$.
LV = left ventricular.

had normal coronary arteries and received no medication for the duration of the study. At the follow-up evaluation, DDD pacing was discontinued acutely to enable measurements in sinus rhythm.

Signal-averaged electrocardiography was performed using a high-resolution electrocardiogram (Predictor, Corazonix Corporation). Signals were amplified, digitized and averaged to a noise level of <0.5 μV, using a selected template for QRS detection and alignment, and a bidirectional filter with a high-pass corner frequency of 25 Hz. A vector magnitude was plotted combining the filtered outputs of each lead. The following parameters were determined: duration and root-mean-square of the QRS (measured independently in the X, Y and Z axes) and total QRS vector, and also duration of low-amplitude signals (<40 μV).

The coefficient of intrapatient error for signal-averaged parameters measured previously on 2 separate occasions in 30 patients with HC was as follows: filtered QRS duration 4 ms or 3.3%; root-mean-square voltage 3.7 μV or 5.2%; and low-amplitude signals 1.7 ms or 7%.

Echocardiographic studies were performed using a Hewlett-Packard (Sonos 1000) real-time, pulsed array, 90° ultrasonic scanner with a 2.5 Mhz transducer, as previously described.[5–7] Two-dimensional echocardiographic images were obtained in a number of planes using standard transducer positions. Dimensions of the ventricular septum, posterior free wall and cardiac chambers were assessed quantitatively from the M-mode and 2-dimensional echocardiograms.

Data were expressed as mean ± 1 SD. Fisher's exact test and Wilcoxon signed-rank sum were used for comparison of discrete variables.

RESULTS

Symptomatic echocardiographic and hemodynamic change due to chronic dual-chamber pacing: Chronic DDD pacing was associated with significant symptomatic improvement. Of 12 patients in New York Heart Association functional class III at baseline, 9 improved to class I and 3 to class II. All 6 patients in New York Heart Association functional class IV at baseline improved to class II. Figure 1 shows the reduction in LV outflow tract gradient in DDD pacing and in sinus rhythm at follow-up in 1 patient. Table I summarizes the echocardiographic and hemodynamic findings of the patient cohort. There was a small but significant reduction in LV systolic dimension measured echocardiographically ($p < 0.01$). Heart rate at baseline (79 ± 16 beats/min) was not significantly different from that at follow-up measured in sinus rhythm (80 ± 13 beats/min). There was no significant alteration in right heart

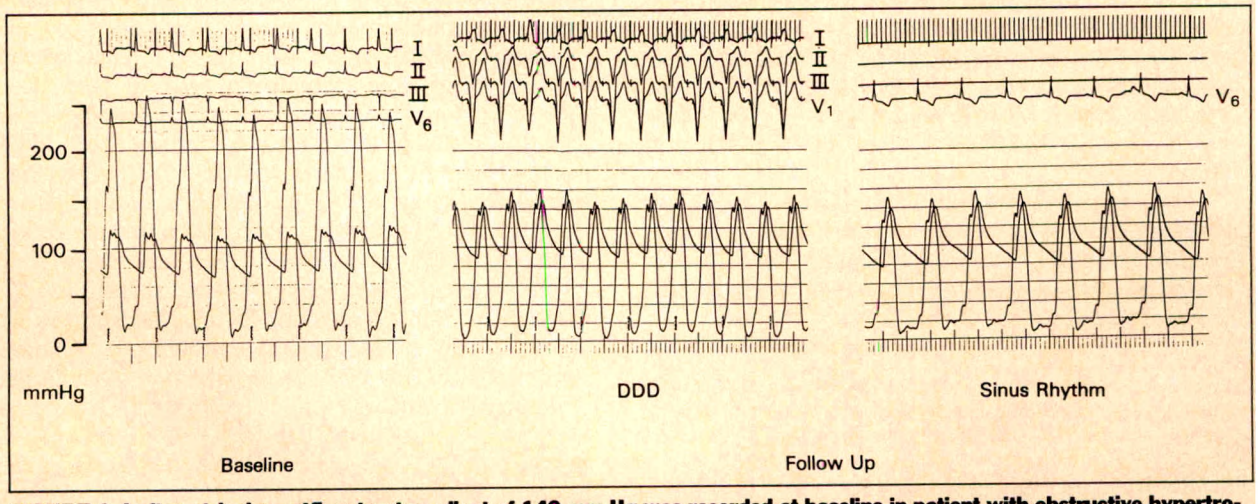


FIGURE 1. Left ventricular outflow tract gradient of 140 mm Hg was recorded at baseline in patient with obstructive hypertrophic cardiomyopathy; after 12 weeks of dual-chamber (DDD) pacing, left ventricular outflow tract gradient was abolished in both dual-chamber pacing mode and sinus rhythm.

pressures or cardiac output in DDD pacing at follow-up compared with baseline measurements. There was a significant decrease in LV outflow tract gradient from 94 ± 47 mm Hg at baseline to 39 ± 51 mm Hg at follow-up in DDD mode ($p < 0.001$; Figure 2). Hemodynamic results at follow-up in sinus rhythm were similar to those in DDD pacing, and mean LV outflow tract gradient (49 ± 45 mm Hg) was significantly ($p < 0.001$) lower than at baseline, but not significantly different from that measured in DDD pacing. LV systolic pressure decreased significantly from 210 ± 43 mm Hg at baseline to 165 ± 58 mm Hg in DDD mode ($p < 0.001$) and 177 ± 56 mm Hg ($p < 0.01$) in sinus rhythm at 12-week follow-up.

Twelve-lead electrocardiographic changes: Figure 3 demonstrates the effect of chronic DDD pacing on the surface 12-lead electrocardiogram recorded in sinus rhythm. There was a small but significant increase in R-wave axis after chronic pacing (37 ± 26° at baseline vs 54 ± 24° after DDD pacing; $p < 0.001$). Figure 4 shows the alteration in amplitude of the R, S and T waves on the surface 12-lead electrocardiogram after pacing. R-wave amplitude was reduced by ≥0.5 mv in 4 patients, unchanged in 12 and increased in 2 in leads $V_{5,6}$. Similarly, the amplitude of the S wave in leads $V_{1,2}$ was reduced by ≥0.5 mv in 7 patients, unchanged in 7 and increased in 4. The T wave became more negative (≥0.1 mv) in leads II, III, aVF and $V_{5,6}$ in 13 patients and more positive in leads I and aVL in 12.

Changes in signal-averaged electrocardiogram: Figure 5 shows the effect of chronic pacing on the signal-averaged electrocardiogram. DDD pacing affected depolarization significantly, as shown by the diverse changes in the duration and root-mean-square of QRS measured on the filtered X, Y and Z axes, and of total QRS and low-amplitude signals (Figure 6). The only significant directional change was an increase in the duration of total QRS (106 ± 12 ms at baseline vs 112 ± 13 ms at follow-up; $p = 0.036$; Figure 6). Furthermore, the root-mean-square of the Y axis increased almost to significance (170 ± 82 vs 195 ± 102 μV; $p = 0.059$). Mean noise level was 0.30 ± 0.00 μV at baseline and 0.34 ± 0.10 μV at follow-up.

There was no significant relation between the electrical changes in the surface 12-lead electrocardiogram and the mechanical change in LV function assessed by correlations between change in the amplitude of the S wave in $V_{1,2}$ or the summated change of S wave in V_1

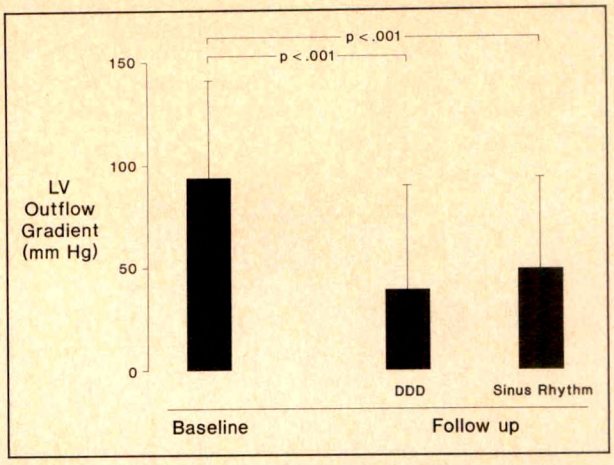


FIGURE 2. Effect of chronic dual-chamber (DDD) pacing on left ventricular (LV) outflow tract gradient in 18 patients with obstructive hypertrophic cardiomyopathy. There was a significant reduction in gradient comparing baseline measurements with those at follow-up in dual-chamber pacing and sinus rhythm.

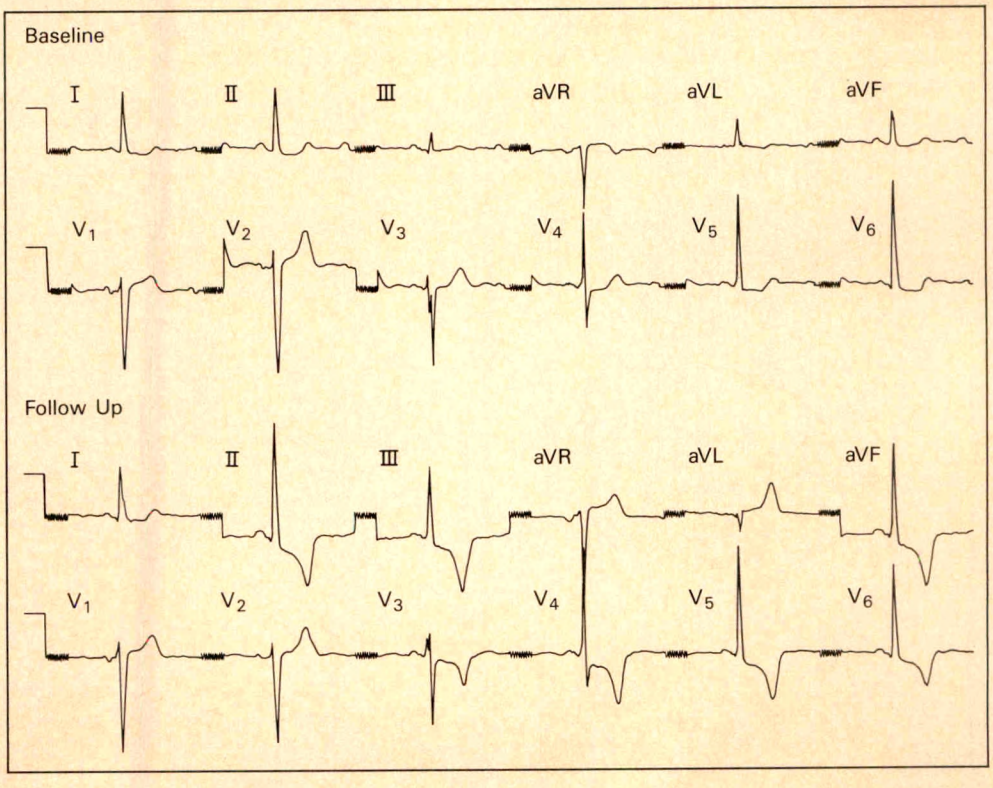
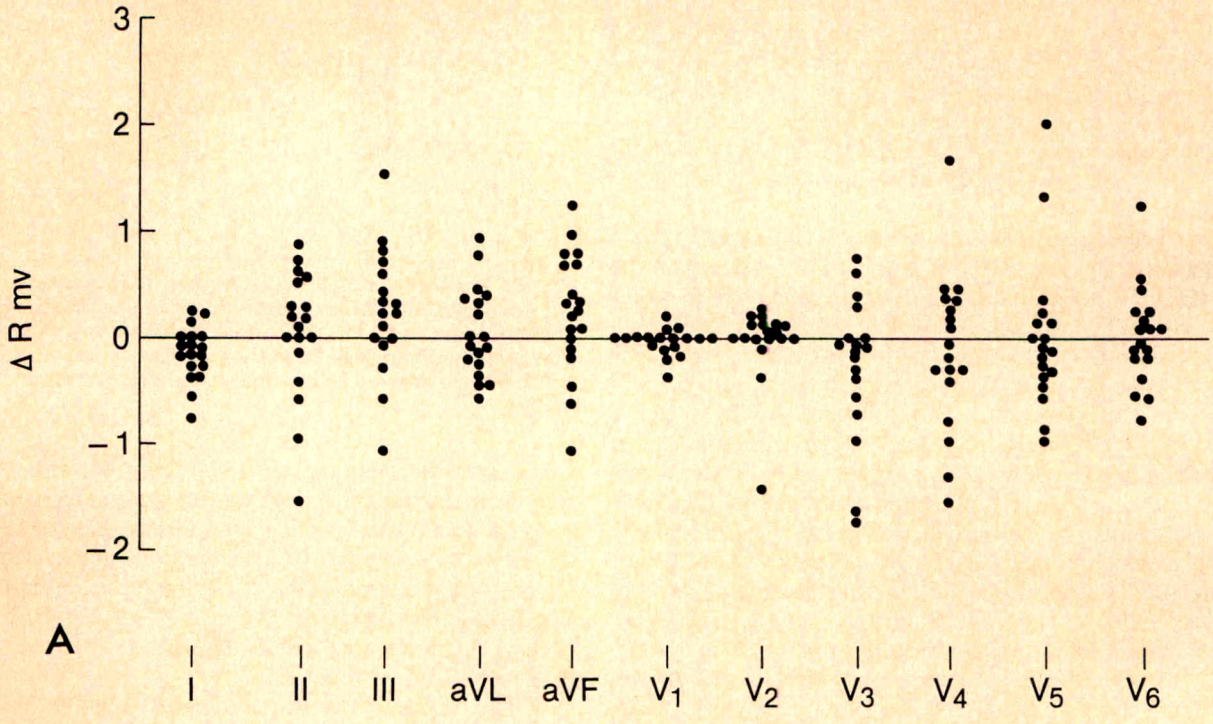
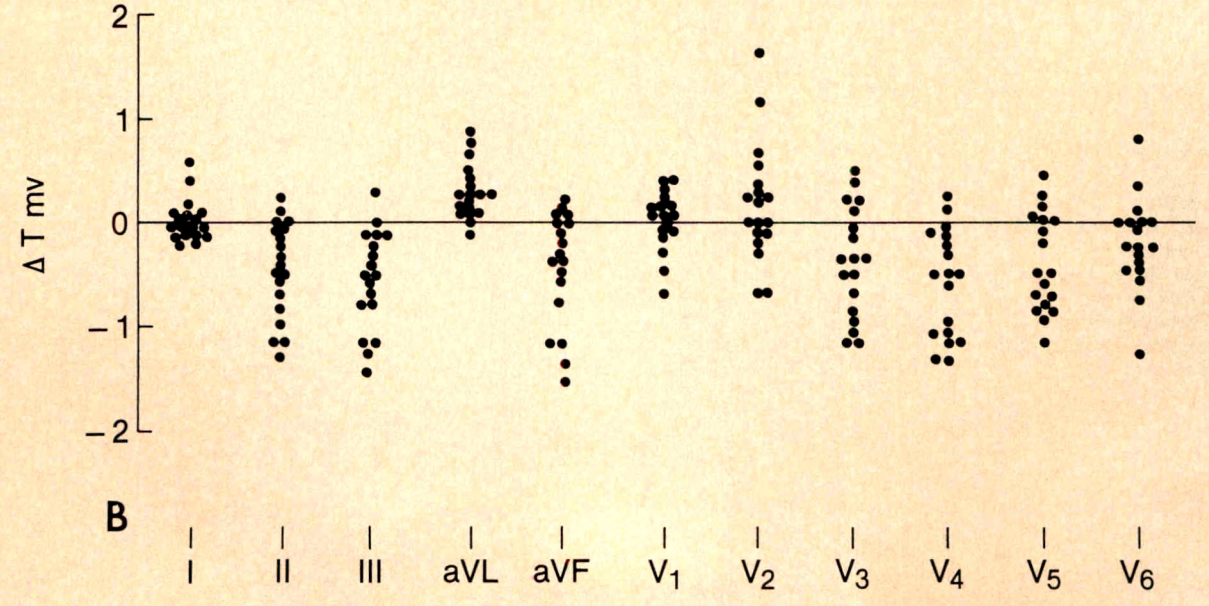


FIGURE 3. Effect of chronic dual-chamber pacing on surface 12-lead electrocardiogram in patient with obstructive hypertrophic cardiomyopathy. There are changes in amplitude of R, S and T waves.

	I	II	III	aVL	aVF	V_1	V_2	V_3	V_4	V_5	V_6
Baseline	1.0 ± 0.6	1.6 ± 1.2	0.9 ± 0.9	0.6 ± 0.5	1.2 ± 1.1	0.2 ± 0.3	0.5 ± 0.5	1.0 ± 0.8	1.6 ± 1.2	1.9 ± 1.1	1.9 ± 1.2
Chronic DDD pacing	0.9 ± 0.5	1.6 ± 0.9	1.1 ± 0.9	0.6 ± 0.6	1.4 ± 0.9	0.2 ± 0.2	0.5 ± 0.5	0.8 ± 0.5	1.5 ± 1.0	1.9 ± 1.2	1.9 ± 1.3
	p = 0.03	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS



	I	II	III	aVL	aVF	V_1	V_2	V_3	V_4	V_5	V_6
Baseline	0.0 ± 0.2	0.0 ± 0.4	0.1 ± 0.2	−0.1 ± 0.2	0.0 ± 0.4	0.2 ± 0.2	0.4 ± 0.6	0.3 ± 0.7	0.2 ± 0.7	0.0 ± 0.6	−0.1 ± 0.5
Chronic DDD pacing	0.0 ± 0.2	−0.3 ± 0.7	−0.5 ± 0.6	0.3 ± 0.3	−0.4 ± 0.6	0.3 ± 0.3	0.5 ± 0.6	−0.1 ± 0.7	−0.4 ± 0.7	−0.4 ± 0.6	−0.3 ± 0.5
	NS	p 0.05	p<0.001	p<0.001	p<0.001	NS	NS	p<0.01	p<0.001	p<0.01	p<0.01



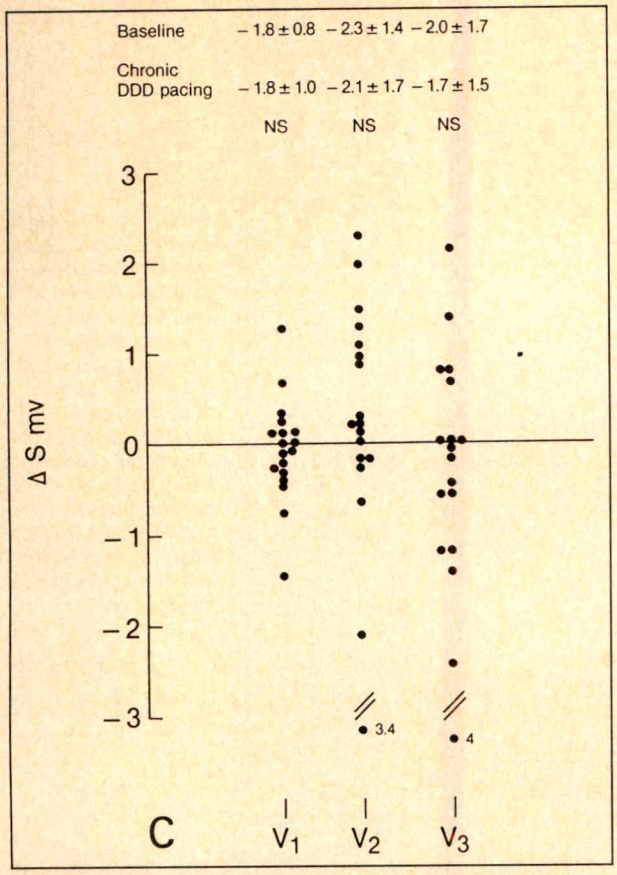


FIGURE 4. Change in amplitude of *(A)* R, *(B)* T and *(C)* septal S waves on surface electrocardiogram after chronic dual-chamber (DDD) pacing. There are bidirectional alterations in amplitude, with significant directional changes in leads I and aVL, and inferior leads. NS = not significant.

and R wave in V_5, and reduction in LV outflow tract gradient or LV systolic pressure measured in sinus rhythm.

DISCUSSION

This study confirms that DDD pacing reduces LV outflow tract gradient significantly in patients with obstructive HC and results in significant symptomatic improvement. DDD pacing for outflow obstruction is cost-effective and is associated with less morbidity and mortality than is cardiac surgery. The mechanism of reduction in LV outflow tract gradient may be due in part to induction of paradoxical movement of the ventricular septum.[1] However, an unexpected finding has been that the reduction in obstruction to LV outflow persists in sinus rhythm after cessation of pacing. This suggests that the reduction in outflow obstruction is not solely due to the mechanical effects of right ventricular and ventricular septal preexcitation.

The hemodynamic changes are accompanied by significant changes in depolarization and repolarization, as recorded by surface 12-lead and signal-averaged electrocardiography. The repolarization (T-wave) changes are similar to those reported previously in normal subjects.[3] However, the time course of onset of the electrocardiographic changes is not known. In previous observations, the development and regression of the electrocardiographic changes were related to the rate of pacing. Comparable data are not available in the present study.

Abnormalities of the signal-averaged electrocardiogram have been reported in a wide variety of cardiac conditions including ischemic heart disease and HC.[8–10] The main interest has been in their predictive value for

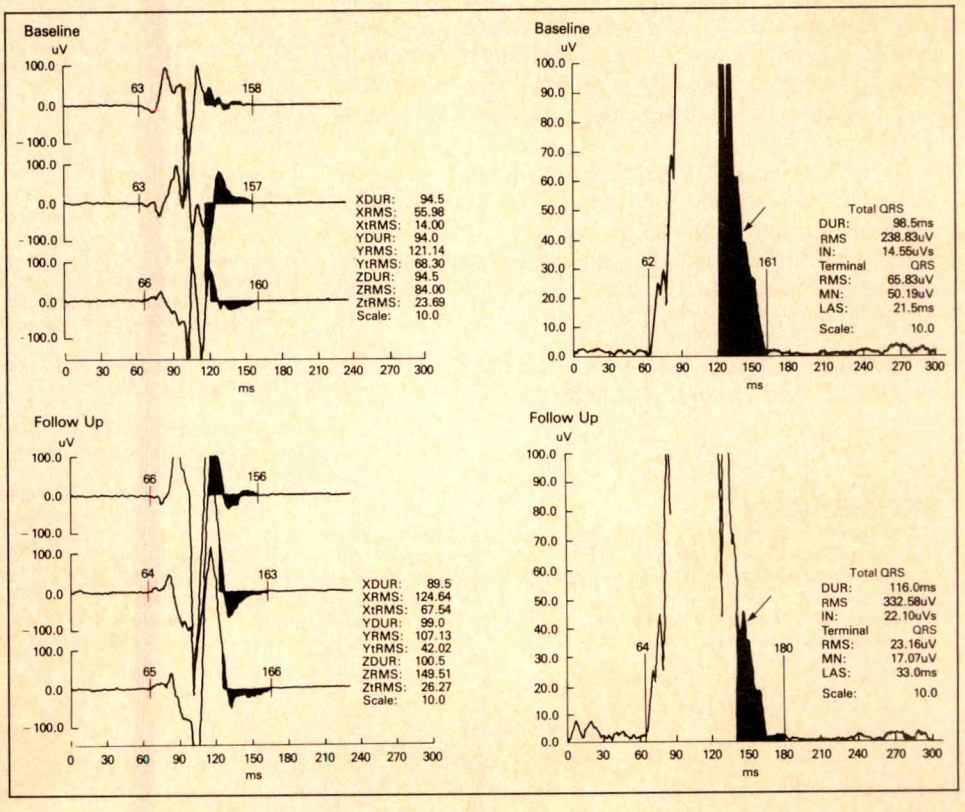


FIGURE 5. Signal-averaged electrocardiogram in patient with obstructive hypertrophic cardiomyopathy showing changes in duration (DUR) and root-mean-square (RMS) of QRS on X, Y and Z axes and in duration of total QRS and low-amplitude signals (LAS), comparing baseline electrocardiogram with that recorded after dual-chamber pacing for 12 weeks. IN = integral voltage; MN = mean.

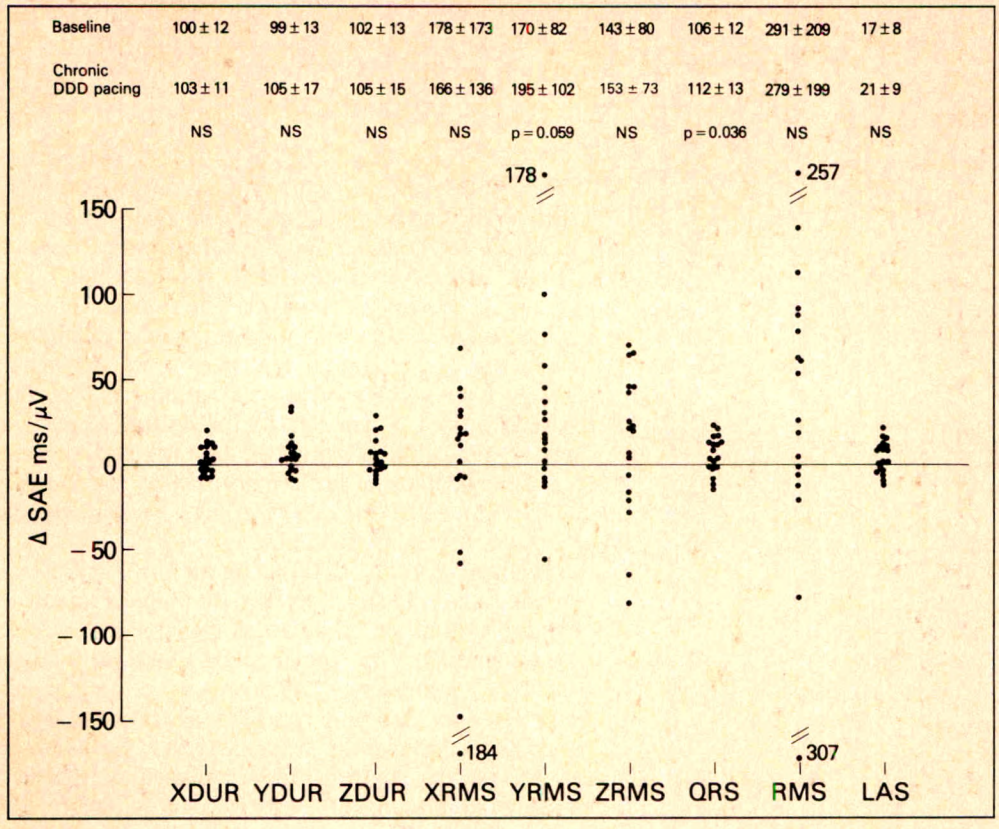


FIGURE 6. Change in duration (DUR) and root-mean-square (RMS) of filtered X, Y and Z axes and QRS, and also change in low-amplitude signal (LAS) after chronic dual-chamber (DDD) pacing. There are bidirectional changes with significant directional change in duration of total QRS. Δ SAE = change in signal-averaged electrocardiogram.

later onset of ventricular tachycardia or fibrillation. Although there was no overall evidence of an increase or decrease in late potentials and thus of altered myocardial arrhythmogenicity, this study shows that the altered hemodynamic state in sinus rhythm after chronic DDD pacing is accompanied by electrical depolarization as well as repolarization changes. The absence of significant directional change in the components of the signal-averaged electrocardiogram is probably due to the wide range of baseline electrocardiographic findings present in HC.

It is known that the cellular/molecular structure of the heart is plastic.[11–14] Hence, the hemodynamic changes after chronic DDD pacing may be explained by induction of myocardial changes at a cellular or molecular level in response to altered myocardial electrical activation or reduction in LV pressures, or both.

Acknowledgment: We thank Julio Panza, MD, for analysis of echocardiographic data.

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Long-Term Follow-Up of Patients Undergoing Myotomy/Myectomy for Obstructive Hypertrophic Cardiomyopathy

Lawrence H. Cohn, MD, Hemant Trehan, MD, and John J. Collins, Jr., MD

The long-term results of patients undergoing myotomy/myectomy of the ventricular septum for obstructive hypertrophic cardiomyopathy are documented in 31 patients (15 women, 16 men, age range 21 to 80 years [mean 55]) with mean New York Heart Association functional class III to IV congestive heart failure, who underwent radical myotomy/myectomy at the Brigham and Women's Hospital from 1972 to 1991. Preoperative gradients by catheterization or echocardiography ranged from 26 to 240 mm Hg (average 96). There were no operative deaths. Two patients developed early postoperative complete heart block requiring a transvenous pacemaker. Clinical follow-up was 1 to 14 years (mean 6.5). All surviving patients were restudied by echocardiography and clinical examination. The mean postoperative functional class was II. Postoperative gradients ranged from 0 to 30 mm Hg (mean 4.5) ($p < 0.001$ compared with preoperative values). There were 5 late deaths (low cardiac output in 2, stroke in 2, and acute respiratory failure in 1); 4 of 5 deaths occurred in patients with concomitant coronary artery disease. Survival at 10 years was 86 ± 9%. There were no reoperations for subaortic obstruction.

(Am J Cardiol 1992;70:657–660)

Approximately 15% of patients with obstructive hypertrophic cardiomyopathy (HC) require surgical intervention.[1] The surgical branch of the National Heart, Lung, and Blood Institute headed by Dr. Glenn Morrow, beginning in the early 1960s, refined surgical approaches to treat hypertrophic subaortic stenosis causing left ventricular outflow tract obstruction. They surgically treated a large group of patients with HC, eventually developing the double myotomy/myectomy operation of the hypertrophic ventricular septum, which effectively ablates the ventricular septal/papillary muscle gradient obstruction with preservation of the mitral valve in patients in whom the mitral valve was normal.[2] A number of other surgical approaches over the years have been advocated for HC including a right-sided approach,[3] a transventricular approach,[4] and mitral valve replacement,[5] but, in fact, none had the simplicity and consistent effectiveness of the transaortic septal approach and none has stood the test of time in terms of relief of left ventricular obstruction and improved long-term survival. Despite the interesting diagnostic and medical published reports associated with this lesion, there have been relatively few long-term follow-up studies of patients who have undergone the Morrow procedure for HC. The experience reported here summarizes data in 31 patients who underwent this procedure over a 15-year period. All patients had been followed up in the postoperative period by echocardiography, and as undergone clinical examination to determine the long-term effectiveness of this procedure.

METHODS

Thirty-one patients (15 women and 16 men, age range 21 to 80 years [mean 55]) with HC underwent operation by the myotomy/myectomy technique between 1977 and 1991 at the Brigham and Women's Hospital. Preoperative New York Heart Association functional class averaged III to IV. There were 2 patients in functional class II, 24 in functional class III and 5 in functional class IV. Preoperative atrial fibrillation was noted in 16 patients. Patients with HC not treated by this specific surgical technique or in whom a combination of techniques was used were not included.

In all patients preoperative septal thickness was >20 mm measured by echocardiography. Preoperative mitral regurgitation was present in 19 of 31 patients: 1+ in 10 patients, 2+ in 7, 3+ in 1, and 4+ in 1. The resting left ventricular gradients across the left ventricular subaortic obstruction ranged from 26 to 240 mm Hg (aver-

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age 96). The gradients were measured by preoperative simultaneous left ventricular and aortic catheters, by pullback (all patients) and, most recently, with echocardiography.

All patients underwent operation with the use of cardiopulmonary bypass and underwent transaortic radical myotomy/myectomy similar to the procedure described by Morrow.[6] The anterior leaflet of mitral valve and papillary muscle are protected inferiorly by a malleable brain retractor, and a sponge stick helps to evert the septum into the outflow tract. The right coronary aortic leaflet is retracted with another smaller malleable brain retractor. The first septal incision is made approximately at the midportion of the distance underneath the right coronary aortic leaflet, and a second myotomy made to the left of this about 1 cm in width to prevent the production of complete heart block by injuring the bundle of His. The myotomy is then carried down through the hypertrophic septum into free left ventricular cavity with both myotomies. By a combination of sharp dissection and debridement with a pituitary rongeur, a large channel through the hypertrophic muscle is created by resection of this muscle block. All muscle bundles toward the free wall are liberated and resected. This channel is then in opposition to the anterior leaflet of the mitral and the papillary muscle which form the other part of this funnel-shaped obstructive area.

In addition to this procedure, 8 patients underwent surgical procedures: 6 patients had a concomitant coronary bypass, and 2 patients had aortic and mitral valvuloplasty. Patients in chronic atrial fibrillation underwent anticoagulation postoperatively with warfarin, and those with coronary disease requiring coronary artery bypass were prescribed 1 aspirin per day.

All patients were followed with periodic echocardiogram and clinical examination by their cardiologists, and were called back for a functional evaluation beginning in the late spring of 1991. Follow-up echocardio-

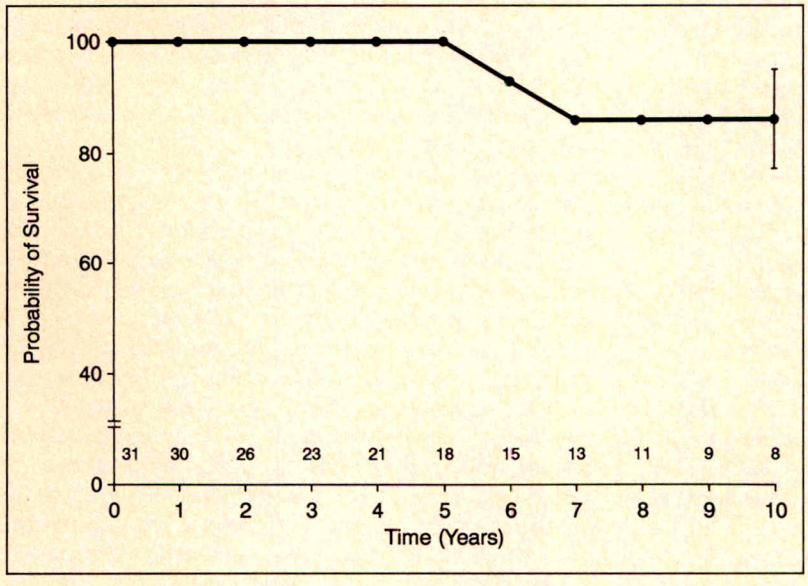


FIGURE 1. Actuarial survival of patients after hypertrophic septal myotomy/myectomy.

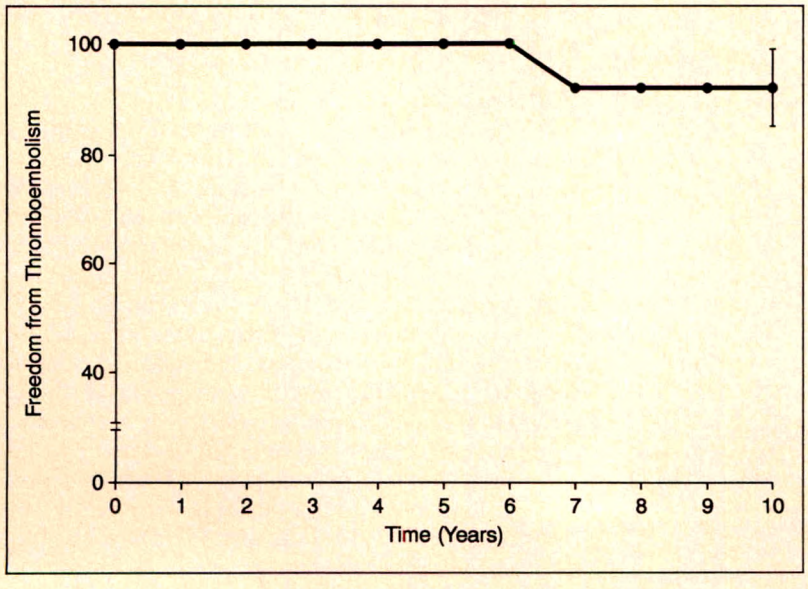


FIGURE 2. Actuarial probability of freedom from thromboembolism in patients after myotomy/myectomy.

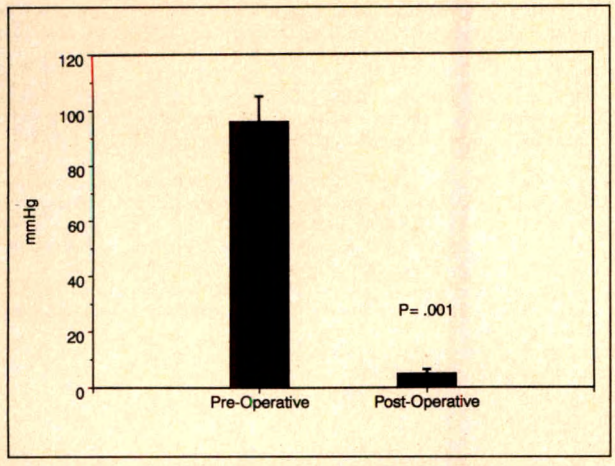


FIGURE 3. Pre- and postoperative gradient (mm Hg) measurements after septal myotomy/myectomy for hypertrophic cardiomyopathy.

grams were recorded in all patients to determine the extent of any residual subaortic obstruction.

RESULTS

There was no operative mortality. Two patients developed complete heart block (8%) after myotomy/myectomy, requiring a permanent transvenous atrioventricular sequential pacemaker. There were no other major early postoperative complications.

Clinical follow-up was 1 to 14 years (mean 6.5). Five patients had late deaths; 4 of these 5 had undergone a concomitant coronary bypass operation and had complete reconstruction. One patients had a single, 3 had a double and 2 had a triple coronary bypass concomitantly. Four of 6 patients who had concomitant coronary bypass grafting died in the late postoperative period. There was only 1 late death occurring in 25 patients who did not have coronary bypass grafting, an incidence of 4% ($p = 0.05$). Two patients with coronary disease died of low cardiac output from restrictive cardiomyopathy 11 and 14 years postoperatively; 2 additional patients with coronary artery disease died of stroke 7 and 12 years postoperatively, and 1 patient with coronary disease died of acute respiratory failure. The actuarial survival for all patients was 86 ± 9% (SEM) at 10 years (Figure 1). The probability of freedom from thromboembolism in patients after surgery for HC was 92 ± 7% (Figure 2). The functional classification in the 26 surviving patients was a mean of II; 17 were in functional class I, 6 were in functional class II, and 5 were in functional class III. The patients restudied in the late postoperative period by echocardiography to evaluate subaortic obstruction had gradients ranging from 0 to 30 mm Hg (mean of 4.5; $p < 0.001$ compared with the preoperative values) (Figure 3).

DISCUSSION

This study confirms previous findings in a series by the National Institutes of Health group[7] and by others,[8,9] that the double septal (myotomy/myectomy Morrow) procedure produces a channel in the hypertrophic ventricular septum deep enough and wide enough to eliminate one of the elements of the subaortic stenosis produced in this syndrome. The ablation of left ventricular outflow obstruction was correlated with improvements in patients symptoms in almost every case. Freedom from late death was high, unless the patient had concomitant coronary disease; late deaths occurred in 4 of 6 patients who had concomitant coronary artery disease even though they underwent complete coronary artery bypass grafting.

We believe that this technique is superior to replacement of the mitral valve or other approaches. It has been shown by our group[8] and others[9] that there is significant morbidity with any type of mitral prosthesis inserted, and maintenance of the normal papillary muscle annular continuity appears to be important for normal shape and function of the left ventricle in the long term.[10] Mitral valve replacement is a consideration in HC when the septal thickness is ≤18 mm or there is significant structural mitral valve pathology.[11,12] A major significant associated morbidity is production of complete heart block, which can be obviated by careful attention to anatomic details, particularly when making the first septal incision. If heart block is produced, atrioventricular sequential pacing is important because these patients have a very noncompliant left ventricle; thus, the atrial contribution to left ventricular filling is extremely important for maintaining normal cardiac output.

An accurate diagnosis is of critical importance in managing patients with HC, and is now most accurately assessed by echocardiographic delineation of the hypertrophic septum. Cardiac catheterization is now recommended only when coronary angiograms are needed, e.g., patients aged >40 years. Intraoperatively we have used transesophageal echocardiography to determine the extent of septal myocardial resection, and we believe it is an important adjunct to insure an adequate resection and that mitral regurgitation is relieved.[13]

We conclude that septal myotomy/myectomy is the treatment of choice for HC in its classic version, i.e., with a septum of ≥18 mm thickness. Although the probability of late survival is excellent, the necessity for concomitant coronary bypass definitely suggests a worse prognosis in the late postoperative period, but does not seem to have a significant impact on perioperative risk. The recurrence rate is very low if resection is performed appropriately at the initial operation.

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A NEW TIMESAVING SOLUTION

Activase® (Alteplase) 100 mg vial for added timesaving convenience in the emergency or critical care setting

Rapidly reconstituted

- New 100 mg vial package contains Activase® lyophilized powder, double-sided, sterile, siliconized transfer device, and diluent – all the necessary components in one convenient package
- Utilization of the new, single-vial design and transfer device can reduce the time necessary to reconstitute Activase® by two-thirds[1]

Conveniently administered – can eliminate the need for an IV bag

- Specially designed vial with plastic hanger so vial can be hung for direct infusion



- 100 mg vial must be used with vented IV tubing or vented adapter spike and non-vented IV tubing
- Contents can be transferred to an IV bag if preferred

20 mg and/or 50 mg vials plus new 100 mg vial provide dosing alternatives

- 20 mg and 50 mg vials for accurate dosing in acute myocardial infarction (AMI) for patients <65 kg
- New 100 mg vial permits convenient dosing for patients ≥65 kg with AMI or acute massive pulmonary embolism

Please see brief summary of prescribing information for Activase® on following page.

1. Data on file, Genentech, Inc.

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ACTIVASE®
ALTEPLASE, RECOMBINANT
A TISSUE PLASMINOGEN ACTIVATOR

ACTIVASE® (Alteplase)

Brief Summary

Consult full prescribing information before using.

INDICATIONS AND USAGE: Acute Myocardial Infarction: Activase® is indicated for use in the management of acute myocardial infarction (AMI) in adults for the lysis of thrombi obstructing coronary arteries, the reduction of infarct size, the improvement of ventricular function following AMI, the reduction of the incidence of congestive heart failure and the reduction of mortality associated with AMI. Treatment should be initiated as soon as possible after the onset of AMI symptoms (see CLINICAL PHARMACOLOGY section of full prescribing information).

Pulmonary Embolism: Activase® is indicated in the management of acute massive pulmonary embolism (PE) in adults:

for the lysis of acute pulmonary emboli, defined as obstruction of blood flow to a lobe or multiple segments of the lungs, and

for the lysis of pulmonary emboli accompanied by unstable hemodynamics, e.g., failure to maintain blood pressure without supportive measures.

The diagnosis should be confirmed by objective means, such as pulmonary angiography or noninvasive procedures such as lung scanning.

CONTRAINDICATIONS: Because thrombolytic therapy increases the risk of bleeding, Activase® is contraindicated in the following situations: • Active internal bleeding • History of cerebrovascular accident • Recent (within two months) intracranial or intraspinal, surgery or trauma (see WARNINGS) • Intracranial neoplasm, arteriovenous malformation, or aneurysm • Known bleeding diathesis • Severe uncontrolled hypertension

WARNINGS: Bleeding: The most common complication encountered during Activase® therapy is bleeding. The type of bleeding associated with thrombolytic therapy can be divided into two broad categories: • Internal bleeding, involving the gastrointestinal tract, genitourinary tract, retroperitoneal or intracranial sites. • Superficial or surface bleeding, observed mainly at invaded or disturbed sites (e.g., venous cutdowns, arterial punctures, sites of recent surgical intervention).

The concomitant use of heparin anticoagulation may contribute to bleeding. Some of the hemorrhagic episodes occurred one or more days after the effects of Activase® had dissipated, but while heparin therapy was continuing.

As fibrin is lysed during Activase® therapy, bleeding from recent puncture sites may occur. Therefore, thrombolytic therapy requires careful attention to all potential bleeding sites (including catheter insertion sites, arterial and venous puncture sites, cutdown sites and needle puncture sites).

Intramuscular injections and nonessential handling of the patient should be avoided during treatment with Activase®. Venipunctures should be performed carefully and only as required.

Should an arterial puncture be necessary during an infusion of Activase®, it is preferable to use an upper extremity vessel that is accessible to manual compression. Pressure should be applied for at least 30 minutes, a pressure dressing applied and the puncture site checked frequently for evidence of bleeding.

Should serious bleeding (not controllable by local pressure) occur, the infusion of Activase® and any concomitant heparin should be terminated immediately.

Each patient being considered for therapy with Activase® should be carefully evaluated and anticipated benefits weighed against potential risks associated with therapy.

In the following conditions, the risks of Activase® therapy may be increased and should be weighed against the anticipated benefits: • Recent (within 10 days) major surgery, e.g., coronary artery bypass graft, obstetrical delivery, organ biopsy, previous puncture of noncompressible vessels • Cerebrovascular disease • Recent gastrointestinal or genitourinary bleeding (within 10 days) • Recent trauma (within 10 days) • Hypertension: systolic BP ≥ 180 mm Hg and/or diastolic BP ≥ 110 mm Hg • High likelihood of left heart thrombus, e.g., mitral stenosis with atrial fibrillation • Acute pericarditis • Subacute bacterial endocarditis • Hemostatic defects including those secondary to severe hepatic or renal disease • Significant liver dysfunction • Pregnancy • Diabetic hemorrhagic retinopathy, or other hemorrhagic ophthalmic conditions • Septic thrombophlebitis or occluded AV cannula at seriously infected site • Advanced age, i.e., over 75 years old • Patients currently receiving oral anticoagulants, e.g., warfarin sodium • Any other condition in which bleeding constitutes a significant hazard or would be particularly difficult to manage because of its location

Arrhythmias: Coronary thrombolysis may result in arrhythmias associated with reperfusion. These arrhythmias (such as sinus bradycardia, accelerated idioventricular rhythm, ventricular premature depolarizations, ventricular tachycardia) are not different from those often seen in the ordinary course of acute myocardial infarction and may be managed with standard antiarrhythmic measures. It is recommended that antiarrhythmic therapy for bradycardia and/or ventricular irritability be available when infusions of Activase®, Alteplase, are administered.

Pulmonary Embolism: It should be recognized that the treatment of pulmonary embolism with Activase®, Alteplase, has not been shown to constitute adequate clinical treatment of underlying deep vein thrombosis. Furthermore, the possible risk of reembolization due to the lysis of underlying deep venous thrombi should be considered.

PRECAUTIONS: General: Standard management of myocardial infarction or pulmonary embolism should be implemented concomitantly with Activase® treatment. Noncompressible arterial puncture must be avoided (i.e., internal jugular and subclavian punctures should be avoided to minimize bleeding from noncompressible sites). Arterial and venous punctures should be minimized. In the event of serious bleeding, Activase® and heparin should be discontinued immediately. Heparin effects can be reversed by protamine.

Readministration: There is no experience with readministration of Activase®. If an anaphylactoid reaction occurs, the infusion should be discontinued immediately and appropriate therapy initiated.

Although sustained antibody formation in patients receiving one dose of Activase® has not been documented, readministration should be undertaken with caution. Detectable levels of antibody (a single point measurement) were reported in one patient but subsequent antibody test results were negative.

Laboratory Tests: During Activase® therapy, if coagulation tests and/or measures of fibrinolytic activity are performed, the results may be unreliable unless specific precautions are taken to prevent *in vitro* artifacts. Activase® is an enzyme that when present in blood in pharmacologic concentrations remains active under *in vitro* conditions. This can lead to degradation of fibrinogen in blood samples removed for analysis. Collection of blood samples in the presence of aprotinin (150-200 units/mL) can to some extent mitigate this phenomenon.

Drug Interactions: The interaction of Activase® with other cardioactive drugs has not been studied. In addition to bleeding associated with heparin and vitamin K antagonists, drugs that alter platelet function (such as acetylsalicylic acid, dipyridamole) may increase the risk of bleeding if administered prior to, during or after Activase® therapy.

Use of Anticoagulants: Heparin has been administered concomitantly with and following infusions of Activase® to reduce the risk of rethrombosis. Because either heparin or Activase® alone may cause bleeding complications, careful monitoring for bleeding is advised, especially at arterial puncture sites.

Pregnancy (Category C): Animal reproduction studies have not been conducted with Activase®. It is also not known whether Activase® can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Activase® should be given to a pregnant woman only if clearly needed.

Pediatric Use: Safety and effectiveness of Activase® in children has not been established.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies in animals have not been performed to evaluate the carcinogenic potential or the effect on fertility. Short-term studies, which evaluated tumorigenicity of Activase® and effect on tumor metastases in rodents, were negative.

Studies to determine mutagenicity (Ames test) and chromosomal aberration assays in human lymphocytes were negative at all concentrations tested. Cytotoxicity, as reflected by a decrease in mitotic index, was evidenced only after prolonged exposure and only at the highest concentrations tested.

Nursing Mothers: It is not known whether Activase® is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Activase®, Alteplase, is administered to a nursing woman.

ADVERSE REACTIONS: Bleeding: The most frequent adverse reaction associated with Activase® is bleeding. The type of bleeding associated with thrombolytic therapy can be divided into two broad categories: • Internal bleeding, involving the gastrointestinal tract, genitourinary tract, retroperitoneal or intracranial sites. • Superficial or surface bleeding, observed mainly at invaded or disturbed sites (e.g., venous cutdowns, arterial punctures, sites of recent surgical intervention).

The following incidence of significant internal bleeding (estimated as >250 cc blood loss) has been reported in studies in over 800 patients treated at all doses:

	Total Dose ≤ 100 mg	Total Dose > 100 mg
gastrointestinal	5%	5%
genitourinary	4%	4%
ecchymosis	1%	<1%
retroperitoneal	<1%	<1%
epistaxis	<1%	<1%
gingival	<1%	<1%

The incidence of intracranial bleeding (ICB) in patients treated with Activase® is as follows:

Dose	Number of Patients	%
100 mg	3272	0.4
150 mg	1779	1.3
1-1.4 mg/kg	237	0.4

These data indicate that a dose of 150 mg of Activase® should not be used because it has been associated with an increase in intracranial bleeding.

Recent data indicate that the incidence of stroke in 6 randomized double-blind placebo controlled trials[1-7] is not significantly different in the Activase® treated patients compared to those treated with placebo (37/3161, 1.2% versus 27/3092, 0.9%, respectively)(p = 0.26).

Should serious bleeding in a critical location (intracranial, gastrointestinal, retroperitoneal, pericardial) occur, Activase® therapy should be discontinued immediately, along with any concomitant therapy with heparin.

ACTIVASE® (Alteplase)

Fibrin which is part of the hemostatic plug formed at needle puncture sites will be lysed during Activ therapy. Therefore, Activase® therapy requires careful attention to potential bleeding sites, e.g., catheter inse sites, arterial puncture sites.

Allergic Reactions: No serious or life-threatening allergic reactions have been reported. Other hypersensitivity reactions such as urticaria have been observed occasionally.

Other Adverse Reactions: Other adverse reactions have been reported, principally nausea and/or vomi hypotension, and fever. These reactions are frequent sequelae of myocardial infarction and may or may nc attributable to Activase® therapy.

DOSAGE AND ADMINISTRATION: Activase® is for intravenous administration only.

Acute Myocardial Infarction: Administer Activase® as soon as possible after the onset of symptor

The recommended dose is 100 mg administered as 60 mg (34.8 million IU) in the first hour (of which 6 to 1C is administered as a bolus over the first 1-2 minutes), 20 mg (11.6 million IU) over the second hour, and 20 (11.6 million IU) over the third hour. For smaller patients (less than 65 kg), a dose of 1.25 mg/kg administered 3 hours, as described above, may be used.[8]

a. The bolus dose may be prepared in one of the following ways:
   1. By removing 6 to 10 mL from the vial of reconstituted (1 mg/mL) Activase® using a syringe and needle this method is used with the 20 mg or 50 mg vials, the syringe should not be primed with air and the ne should be inserted into the Activase® vial stopper. If the 100 mg vial is used, the needle should be inse away from the puncture mark made by the transfer device.
   2. By removing 6 to 10 mL from a port (second injection site) on the infusion line after the infusion se primed.
   3. By programming an infusion pump to deliver a 6 to 10 mL (1 mg/mL) bolus at the initiation of the infusior

b. The remainder of the Activase® dose may be administered as follows:

20 mg, 50 mg vials, administer using either a polyvinyl chloride bag or glass vial and infusion set.

100 mg vials, insert the spike end of an infusion set through the same puncture site created by the tran device in the stopper of the vial of reconstituted Activase®. Hang the Activase® vial from the plastic mol capping attached to the bottom of the vial.

Although the use of anticoagulants and antiplatelet drugs during and following administration of Activase® not been shown to be of unequivocal benefit, heparin has been administered concomitantly for 24 hours or longe more than 90% of patients. Aspirin and/or dipyridamole have been given either during and/or following hepa treatment.

Pulmonary Embolism: The recommended dose is 100 mg administered by intravenous infusion over two hou Heparin therapy should be instituted or reinstituted near the end of or immediately following the Activase® infus when the partial thromboplastin time or thrombin time returns to twice normal or less.

The dose may be administered using the instructions described above in Acute Myocardial Infarction (b).

A DOSE OF 150 MG OF ACTIVASE®, ALTEPLASE, SHOULD NOT BE USED BECAUSE IT HAS BE ASSOCIATED WITH AN INCREASE IN INTRACRANIAL BLEEDING.

Reconstitution and Dilution: Activase® should be reconstituted by aseptically adding the appropriate volume the accompanying Sterile Water for Injection, USP to the vial. It is important that Activase® be reconstituted o with Sterile Water for Injection, USP, without preservatives. Do not use Bacteriostatic Water for Injection, USP. T reconstituted preparation results in a colorless to pale yellow transparent solution containing Activase® 1 mg/mL approximately pH 7.3. The osmolality of this solution is approximately 215 mOsm/kg.

Because Activase® contains no antibacterial preservatives, it should be reconstituted immediately before u The solution may be used for intravenous administration within 8 hours following reconstitution when stor between 2-30°C (36-86°F). Before further dilution or administration, the product should be visually inspected particulate matter and discoloration prior to administration whenever solution and container permit.

Activase® may be administered as reconstituted at 1 mg/mL. As an alternative, the reconstituted solution may diluted further immediately before administration in an equal volume of 0.9% Sodium Chloride Injection, USP 5% Dextrose Injection, USP to yield a concentration of 0.5 mg/mL. Either polyvinyl chloride bags or glass vials a acceptable. Activase® is stable for up to 8 hours in these solutions at room temperature. Exposure to light has effect on the stability of these solutions. Excessive agitation during dilution should be avoided; mixing should accomplished with gentle swirling and/or slow inversion. Do not use other infusion solutions, e.g., Sterile Water Injection, USP or preservative-containing solutions for further dilution.

20 mg and 50 mg vials: Reconstitution should be carried out using a large bore needle (e.g., 18 gauge) a a syringe, directing the stream of Sterile Water for Injection, USP into the lyophilized cake. **DO NOT USE VACUUM IS NOT PRESENT.** Slight foaming upon reconstitution is not unusual; standing undisturbed several minutes is usually sufficient to allow dissipation of any large bubbles.

No other medication should be added to infusion solutions containing Activase®, Alteplase. A unused infusion solution should be discarded.

100 mg vials: Reconstitution should be carried out using the transfer device provided, adding the contents the accompanying 100 mL vial of Sterile Water for Injection, USP to the contents of the 100 mg vial of Activas powder. Slight foaming upon reconstitution is not unusual; standing undisturbed for several minutes is usua sufficient to allow dissipation of any large bubbles. Please refer to the accompanying Instructions for Reconstituti and Administration. **100 MG VIALS DO NOT CONTAIN VACUUM.**

100 MG VIAL RECONSTITUTION

1. Use aseptic technique throughout.
2. Remove the protective flip-caps from one vial of Activase® and one vial of Sterile Water for Injection, US (SWFI).
3. Open the package containing the transfer device by peeling the paper label off the package.
4. Remove the protective cap from one end of the transfer device and keeping the vial of SWFI upright, insert tl piercing pin vertically into the center of the stopper of the vial of SWFI.
5. Remove the protective cap from the other end of the transfer device. **DO NOT INVERT THE VIAL OF SWFI.**
6. Holding the vial of Activase® upside-down, position it so that the center of the stopper is directly over tl exposed piercing pin of the transfer device.
7. Push the vial of Activase® down so that the piercing pin is inserted through the center of the Activase® vi stopper.
8. Invert the two vials so that the vial of Activase® is on the bottom (upright) and the vial of SWFI is upside-dow allowing the SWFI to flow down through the transfer device. Allow the entire contents of the vial of SWFI to flc into the Activase® vial (approximately 0.5 cc of SWFI will remain in the diluent vial). Approximately two minut are required for this procedure.
9. Remove the transfer device and the empty SWFI vial from the Activase® vial. Safely discard both the transf device and the empty diluent vial according to institutional procedures.
10. Swirl gently to dissolve the Activase® powder. **DO NOT SHAKE.**

No other medication should be added to infusion solutions containing Activase®, Alteplase. Ar unused infusion solution should be discarded.

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Do not use beyond the expiration date stamped on the vial.

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Revised January 199
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1,000 Consecutive Children with a Cardiac Malformation with 26- to 37-Year Follow-Up

James H. Moller, MD, and Ray C. Anderson, MD, PhD

The current status of 997 of 1,000 consecutive children with a cardiac malformation initially evaluated between 1952 and 1963 was determined. Of the 1000, 285 have died and the survivors have been followed up for periods of 26 to 37 years. Six hundred thirty-two are in excellent or good clinical condition, being asymptomatic and without planned need for further treatment. The other 80 have significant abnormalities, although 63 of these have few symptoms. Infective endocarditis occurred in 12 of 10,000 susceptible patient-years, with a lower rate in the past decade. Only 22 of the survivors are currently receiving cardiac medication. These data are derived from a group of patients initially seen during a period of time that cardiac surgery was being developed for congenital heart disease. Thus, the outlook should be even better for children who are currently undergoing treatment.

(Am J Cardiol 1992;70:661–667)

The management of children with a cardiac malformation is hampered by a paucity of information about the long-term clinical course of children, whether or not they have undergone cardiac surgery. The "Natural History Study" has provided valuable and important information about the course of patients with ventricular septal defect (VSD), aortic stenosis or pulmonary stenosis,[1] but the number of lesions and the length of follow-up are limited. An ideal study would follow an entire cohort of children with a cardiac malformation from birth into adulthood, but such information has not been reported to our knowledge. Previously, we described 1,000 consecutive children with a cardiac malformation referred to one us (RCA), who were followed for at least 10 years.[2] Subsequently, we have observed this group of 1,000 patients for at least another decade. We determined the survival pattern, clinical course and status of survivors to understand better the course of children with a cardiac malformation.

METHODS

Case records of 1,000 children with a cardiac malformation initially evaluated between March 1952 and December 1963 were reviewed. The group of patients included all children with a cardiac malformation referred to one of us (RCA) for evaluation from the usual geographic referral areas of Minnesota, North and South Dakota, and parts of Iowa, Michigan, Montana, and Wisconsin. Patients living outside this area or who were referred specifically for cardiac surgery were excluded. This study group represents approximately one-third of the children with a cardiac malformation examined by the staff of the pediatric cardiology service at the University of Minnesota during that period of time from the described referral area. Those without cardiac disease who were seen during the same interval are not included in this report.

The current study was begun in 1986 and completed in December 1989. Data were obtained from hospital medical records, patients' physicians, patients, family members, health and governmental agencies. Usually data about any patient was gathered from several sources.

The study, because it involves patients referred during the period of 1952 to 1963, includes the period immediately before and during the development and application of cardiac surgery at the University of Minnesota Hospital.

RESULTS

Current information was obtained about 997 of the 1,000 patients. Three patients, each with an initial diagnosis of small VSD, were lost to follow-up in the years

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TABLE I Summary of 1,000 Consecutive Children with a Cardiac Malformation*

Diagnosis	Pt. No.	Females	Years	Living					Dead				Cause of Death					Current Clinical Status			
				No. Living	Duration of Follow-Up (yr)	Current Age (yr)	Total Years	LTF	No. Dead	Age (yr)	No. Operated	Total Years	Surg.	Heart	Heart + Other	Other	Unknown	Ex.	Good	Fair	Poor
VSD	262	143	6,689	230	28	33	6,494	3	29	8	16	195	11	2	8	7	1	115	105	5	5
VSD+	64	35	1,450	41	31	33	1,349	—	23	5	16	101	9	7	3	2	2	5	30	6	—
PDA	89	67	2,900	85	34	34	2,850	—	4	13	1	50	0	1	0	3	0	83	1	1	—
PDA+	13	8	332	10	31	32	305	—	3	9	1	27	0	1	1	0	1	—	9	1	—
AS	62	19	1,751	53	30	35	1,606	—	9	22	4	145	2	0	0	3	4	—	41	11	1
AS+	13	4	185	5	30	37	152	—	8	6	3	33	3	4	1	0	0	—	5	—	—
PS	72	37	2,006	67	30	36	1,976	—	6	7	4	30	4	1	0	0	1	—	66	1	—
PS+	23	10	567	20	28	32	552	—	3	4	3	15	3	0	0	0	0	—	19	—	1
ASD	41	22	1,160	39	30	35	1,159	—	2	2	2	1	2	0	0	0	0	32	5	2	—
ASD+	12	5	334	10	31	25	310	—	2	13	1	24	0	0	0	1	1	4	5	—	—
Coarctation	34	10	959	31	30	35	932	—	3	14	3	27	1	1	0	1	0	0	27	4	—
Coarctation+	18	9	432	14	31	35	430	—	4	0.6	2	2	2	1	0	1	0	—	12	2	—
AVSD	44	28	616	19	29	31	541	—	25	6	10	75	10	10	4	1	0	3	8	6	2
TOF	75	34	1,400	37	31	33	1,160	—	38	8	26	240	20	8	0	10	0	1	29	4	3
TOF + PA	11	6	74	2	27	30	54	—	9	3	2	20	2	6	0	1	0	—	—	2	—
TGV	19	8	40	1	35	35	35	—	18	0.25	3	5	3	15	0	0	0	—	1	—	—
TGV + VSD	27	15	271	6	28	29	169	—	21	5	13	102	12	9	0	0	0	—	1	2	3
SV	22	14	285	6	32	32	190	—	16	6	5	95	3	10	2	0	1	—	—	6	—
TA	12	8	179	5	31	32	155	—	7	3	3	24	2	4	1	0	0	—	—	5	—
TAPVC	10	7	25	0	—	—	—	—	10	3	3	25	3	5	1	1	0	—	—	—	—
CCTV	10	5	210	5	31	33	156	—	5	14	3	54	1	2	1	1	0	—	2	3	—
Other	66	30	909	26	29	32	749	—	40	6	9	160	9	24	3	3	1	11	11	2	2
Total	1,000	524	22,774	712	—	—	21,324	3	285	—	133	1,450	102	111	25	35	12	254	378	63	17

*Includes double-outlet right ventricle, 7; hypoplastic left ventricle, 7; polysplenia syndrome, 7; situs inversus and associated anomalies, 5; asplenia syndrome, 4; mitral stenosis, 4; truncus arteriosus, 4; aorticopulmonary defect, 3; Ebstein's malformation, 3; left ventricular right atrial communication, 3; pulmonary atresia or stenosis with hypoplastic right ventricle, 3; vascular ring, 3; coronary arterial fistula, 2; mitral regurgitation, 2; abdominal coarctation, 1; "absent" left pulmonary artery, 1; aortic regurgitation, 1; cor triatriatum, 1; interruption of the aortic arch, 1; left ventricular dysplasia, 1; partial anomalous pulmonary venosus connection, 1; ruptured sinus of Valsalva aneurysm, 1; and tricuspid regurgitation, 1.

AS = aortic stenosis; ASD = atrial septal defect; AVSD = atrioventricular septal defect; CCTV = congenitally corrected transposition of great vessels; Ex. = excellent; LTF = long-term follow-up; PA = pulmonary atresia; PDA = patent ductus arteriosus; PS = pulmonary stenosis; Surg. = surgery; SV = single ventricle; TA = tricuspid atresia; TAPVC = total anomalous pulmonary venous connection; TGV = transposition of great vessels; TOF = tetralogy of Fallot; VSD = ventricular septal defect; + = plus coexistent cardiac malformation.

1970, 1970 and 1980, respectively. The 712 surviving patients have been followed for an interval of 26 to 37 years; the mean time of follow-up of survivors was 30 years. Two hundred eighty-five of the 712 patients have died. A total of 22,774 patient-years has been observed.

Of the 712 living patients, diagnosis was established by a combination of cardiac catheterization and surgery in 306 (43%), a combination of clinical findings and surgery in 101 (14%), catheterization alone in 130 (18%), and by clinical findings, electrocardiograms and chest x-ray in the remaining 175 (25%). The diagnosis was confirmed or established at postmortem examination in 205 (72%) of the 285 patients who died, by cardiac catheterization and surgery in 29 (10%), by cardiac catheterization alone in another 30 patients (10%), and by clinical findings, electrocardiograms and chest x-rays in the remaining 21 (8%).

The relative frequency of cardiac diagnoses among the patients is listed in Table I. Patients were divided into major categories, and the table includes all categories with ≥10 patients. There were 66 patients who were grouped in the category "other," because they had an uncommon cardiac malformation (Table I).

There were 524 female and 476 male patients (Table I). The proportion of female patients was greater among those with patent ductus arteriosus (75%), whereas male patients predominated among those with coarctation of the aorta (71%) and valvar aortic stenosis (69%). For the remaining diagnostic categories the sex ratio did not differ.

Surgical observations: Five hundred fifty-seven patients underwent a cardiac operation, 72 of these at another institution subsequent to their evaluation at the University of Minnesota. A total of 641 operations was performed. Operation was reparative in 513, partially reparative in 80, and palliative in the remaining 48 patients.

Survival: Of the 285 deaths, most were within the first year after referral and only 20 in the last decade of this study (1980 to 1989). Actuarial survival curves are shown in Figures 1 and 2. Details of the patients dying in the 1980s are listed in Table II. Of the 446 who were younger than 1 year when initially evaluated, 198 (44%) have died, but among the 554 who were aged >1 year, only 87 (16%) have died. Of the 467 initially evaluated before 1959, 150 (32%) have died, whereas of the 533 seen in 1959 or later, 135 (25%) have died in the subsequent years.

Causes of death: The causes of death for each of the major cardiac malformations are listed in Table I. Deaths occurred after 102 of 641 operations, yielding an operative mortality of 15%. Surgery was considered the cause of death in 102 of the 285 patients (35%), the cardiac condition itself in 111 (39%), and a combination of the cardiac anomaly and a major noncardiac problem in 25 (9%).

The remaining 47 deaths were from a variety of other causes. There were 12 from nonrespiratory infections, including infective endocarditis in 4 patients, brain abscess in 2, septicemia in 2, and single instances of meningitis, encephalitis, peritonitis and gastroenteritis. Another 7 deaths were from accidents. Three deaths were from malignancies, with 2 instances of leukemia and 1 a glioblastoma. Two deaths were from suicide, and 2 from a cerebrovascular accident. Three died of a complication of cardiac catheterization. Individual deaths were attributed to the following: renal failure secondary to Kimmelstiel-Wilson disease, subarachnoid hemorrhage and drug abuse. In 5 instances the cause and circumstances are unknown to us, and in another 10 asymptomatic patients the death was sudden and without other explanation (discussed in the next section).

Other than deaths caused by accidents or surgery, 21 deaths occurred suddenly, only 2 while in the hospital. None of these deaths occurred during exercise. Ten of these 21 deaths were in patients with either no or minimal symptoms. Four were instances of aortic stenosis. Another patient had a VSD and pulmonary vascular disease. Two other deaths occurred in patients with valvar pulmonary stenosis. The 3 remaining deaths were in asymptomatic postoperative patients, 2 with a repaired VSD and the other with tetralogy of Fallot.

Sudden death also occurred in 10 moderately symptomatic patients: 5 with progressive pulmonary vascular disease and 2 with tetralogy of Fallot. The 3 remaining cases were a 27-year-old man 13 years after repair of tetralogy of Fallot, a 43-year-old man with aortic valve replacement, and a 22-year-old with single ventricle and pulmonary stenosis.

The remaining death was both unexpected and sudden. It occurred in a 2-month-old patient with Down's syndrome who was awaiting hospital discharge 5 days after ligation of a patent ductus arteriosus. At postmortem examination a small VSD was present, but no other findings were present.

Two of these late sudden deaths occurred among the 39 patients who died subsequent to repair of a VSD either as an isolated operation or in conjunction with another procedure such as relief of coexistent pulmonary stenosis. These 2 sudden deaths occurred during the 2,754 patient-years of postoperative follow-up among the 118 patients with these operations.

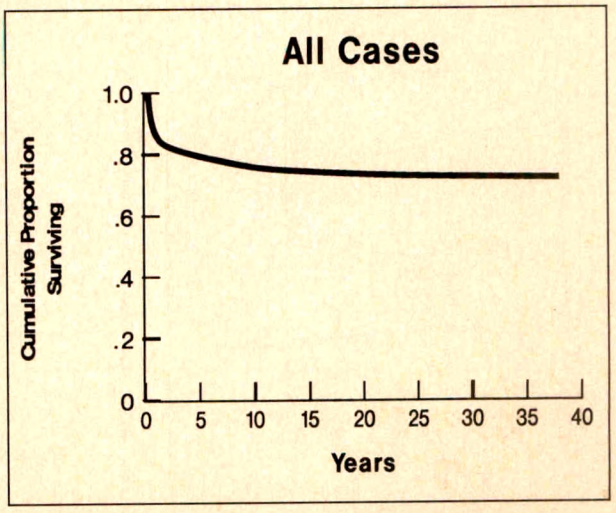


FIGURE 1. Survival of 1,000 consecutive children with a cardiac malformation.

Major medical complications: The history of the patients was reviewed for the major medical problems of infective endocarditis, brain abscess, malignancy, need for cardiac medications and cardiac arrhythmias.

INFECTIVE ENDOCARDITIS: Twenty-one episodes of infective endocarditis occurred, 1 in 2,771 patient-years before our initial evaluation and the other 20 in the 22,774 patient-years after initial evaluation. The rate was 8 of 10,000 patient-years, being 10 of 10,000 for the first 13,860 patient-years and 7 of 10,000 for the last 8,914 patient-years. Twenty cases occurred in 15,481 (13 of 10,000) susceptible postexamination pa-

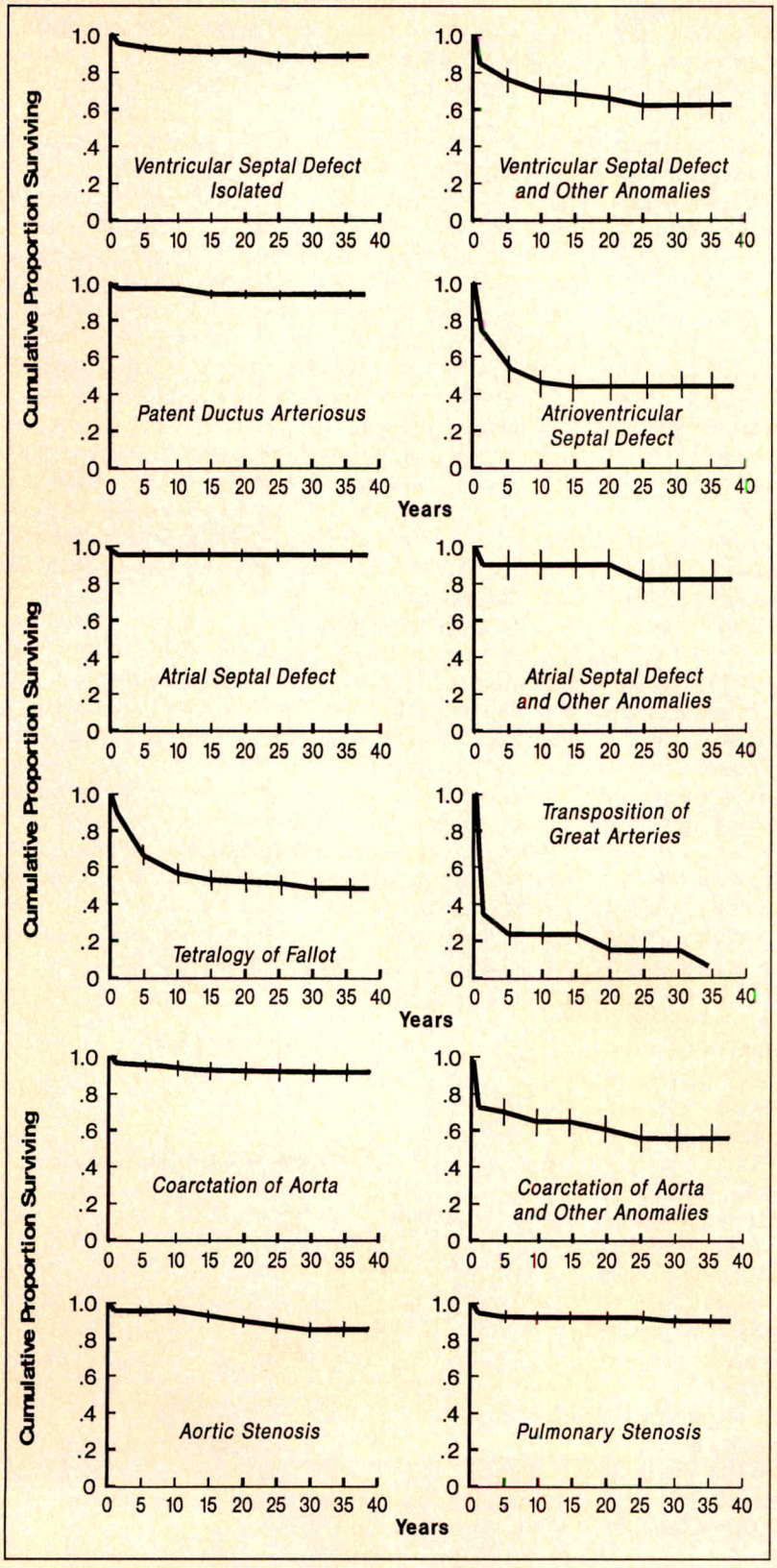


FIGURE 2. Survival of patients with various cardiac malformations.

tient-years (exclusive of 7,293 years after spontaneous or surgical closure of VSD or patent ductus arteriosus or in the presence of nonpredisposing condition, such as isolated situs inversus or pre- or postoperative atrial septal defect). The cardiac malformation associated with infective endocarditis and the respective occurrence rate are listed in Table III.

The 21 episodes occurred in 17 patients, with 1 patient having 2 episodes and another 3 episodes. Recurrences were separated by at least 1 year. Four deaths resulted from infective endocarditis.

BRAIN ABSCESS: Brain abscess occurred in 5 of the 243 patients (2%) with a cardiac malformation associated with a right-to-left shunt, twice in 301 years before initial evaluation and 3 times in 2,131 subsequent patient-years. No episodes have occurred in the last decade. Each of the patients with a brain abscess subsequently underwent a cardiac operation and there were 2 early postoperative deaths. Of the 3 survivors, 2 subsequently developed infective endocarditis, 2 and 16 years later.

MALIGNANCIES: Among the 978 patients without Down's syndrome, 5 malignancies were found during the 22,402 follow-up patient-years. These malignancies were single instances of leukemia, carcinoma of the testicle, glioblastoma, lymphoma, and carcinoma of the thyroid. Only the first 2 patients had undergone cardiac catheterization or angiography. Among the 22 patients with Down's syndrome, 1 instance of leukemia occurred during the 372 follow-up years.

CARDIAC ARRHYTHMIAS: Significant cardiac arrhythmias or heart block were reported in 38 of the 1,000 patients, but the patients have not been systematically studied by continuous electrocardiographic recording or event monitors. Six of the 38 have died. Two deaths were in patients with single ventricle and asymptomatic complete heart block, with deaths occurring at ages of 12 months and 16 years; the latter had severe cardiac failure secondary to the cardiac malformation. Two other deaths occurred in 27-year-old men with postoperative tetralogy of Fallot. One of the 2 had transient heart block after operation, which subsequently became permanent and required pacemaker placement. He died in an auto accident of presumed pacemaker failure. The other patient had cardiomyopathy secondary to operation, recurrent episodes of atrial flutter, and died suddenly. The fifth death occurred in a 2-year-old child with Ebstein's malformation and Wolff-Parkinson-White syndrome, but without rhythm disturbances. The last death was in a 39-year-old patient with corrected transposition of the great arteries and left atrioventricular valve regurgitation who had episodes of atrial flutter and fibrillation and died in congestive cardiac failure.

Ten of the 32 survivors are currently receiving a medication for a cardiac arrhythmia. Ten other patients have a cardiac pacemaker, 6 for heart block after a cardiac operation. In another patient, complete heart block developed 9 years after repair of tetralogy of Fallot at the time of an auto accident. In a patient with corrected transposition and complete heart block, a pacemaker was placed at age 22 years because of symptoms. Another patient with coexistent VSD and subaortic stenosis, who had several cardiac procedures, developed reentrant ventricular tachycardia, and a demand pacemaker was placed. The remaining patient with postoperative atrioventricular septal defect underwent pacemaker placement late postoperatively because of sick sinus syndrome.

TABLE II Deaths Occurring from 1980 to 1989

Diagnosis	Age at Death (year)	Cause
VSD (PO)	22	Accidental
VSD	27	Glioblastoma
VSD + PDA + PS (PO)	26	Died at work
VSD-vascular ring (PO)	18	"Cardiac arrest"
PS + ASD (PO)	25	Sudden
PS	27	Postpartum
AS (PO)	30	Suicide
AS (PO)	43	Sudden
AS	34	Sudden
TOF (PO)	32	Sudden MI
TOF (PO)	29	Drug abuse
TOF (PO)	27	Sudden
DORV	41	PVOD
TGV + VSD (PO)	21	19 days PO
TGV + VSD (PO)	23	1 day PO
SV	24	Respiratory failure
CCT (PO)	39	CHF
SV	22	Sudden
SV-PS	22	1 day PO
PDA + sub. AS	25	Unknown

AS = aortic stenosis; ASD = atrial septal defect; CCT = congenitally corrected transposition of great vessels; CHF = congestive heart failure; DORV = double-outlet right ventricle; MI = myocardial infarction; PDA = patent ductus arteriosus; PO = postoperative; PS = pulmonary stenosis; PVOD = peripheral vascular obstructive disease; sub. AS = subaortic stenosis; SV = single ventricle; TGV = transposition of great vessels; TOF = tetralogy of Fallot; VSD = ventricular septal defect.

TABLE III Occurrence of Infective Endocarditis

Cardiac Condition	No. of Pts.	Total Experience (year)	No. of Endocarditis Episodes	Occurrence Per 10,000 Patients (year)
VSD	262	6,494	2	3
Coarctation	34	959	1	10
AS	62	1,606	4	26
TOF	86	1,160	10	86
TGV	46	206	3	147

AS = aortic stenosis; TGV = transposition of great vessels; TOF = tetralogy of Fallot; VSD = ventricular septal defect.

The remaining 12 patients with a cardiac rhythm disturbance have not required continuing treatment. These include 2 patients with Wolff-Parkinson-White syndrome. Seven other patients developed 1 or more episodes of tachyrhythmia, supraventricular tachycardia (3), atrial flutter (2), atrial fibrillation (1) and ventricular tachycardia (1). Only the last patient required treatment during the 3 years that he had the episodes. One patient, after repair of an atrial septal defect, developed sick sinus syndrome, and another developed complete heart block during a febrile illness and was treated with a temporary pacemaker. The block subsequently resolved, and an electrophysiologic study showed Mobius type I. A patient with corrected transposition developed heart block at age 16 years and is asymptomatic.

Other cardiac medications: Sixteen patients, aged 27 to 52 years, are being treated with a cardiac glycoside and, in several, a diuretic and an afterload reducing agent as well. Ten of these have undergone an operation for a cardiac condition. Four of the 10 patients have complicated VSD, and 2 others have had an aortic valve replacement. The remaining 4 patients had tricuspid valve replacement, Fontan procedure, tetralogy of Fallot repair multiple pacemaker replacements, and postoperative complete transposition. In the other 6 receiving anticongestive therapy, the diagnoses are VSD and pulmonary vascular disease, coexistent VSD and aortic and pulmonary stenosis, complete atrioventricular septal defect and pulmonary vascular disease (n = 2), severe peripheral pulmonary arterial stenosis (pulmonary artery pressure 200 mm Hg) and tetralogy of Fallot and pulmonary atresia.

Current status of surviving patients: The surviving patients were placed into categories according to their current clinical status (Table I):

EXCELLENT: The 254 patients without symptoms, murmurs or cardiomegaly, and a normal electrocardiogram (except for postoperative complete right bundle branch block in some patients) were placed in this category. This included 115 patients with VSD, 83 with patent ductus arteriosus, 32 with atrial septal defect, and 24 with other conditions. Seventy-two of the patients had instances of spontaneous closure of a VSD, a patent ductus arteriosus, or a left ventricular to right atrial shunt. The remaining 182 patients had undergone a cardiac operation.

GOOD: The 378 patients classified as good clinical status have neither symptoms nor cardiomegaly, but have a murmur or an electrocardiographic abnormality. There is neither a significant cardiac abnormality nor a need for a cardiac medication. In this category a variety of cardiac malformations are present, with the largest groups being VSD (105), pulmonary stenosis (66), aortic stenosis (41) and tetralogy of Fallot (27).

FAIR: In 63 patients classified as fair, symptoms were either absent or minimal, but a significant residual cardiac abnormality, a cardiac pacemaker or a prosthetic valve was present.

POOR: In 17 patients there were symptoms and evidence of a definite cardiac abnormality.

DISCUSSION

Several studies have assessed the history of patients with a cardiac malformation[1,2] and have generally considered either specific cardiac anomalies or specific age groups of patients. Our study differs because it represents a follow-up of an unselected group of patients referred to a single pediatric cardiologist for evaluation. Thus, the patient population represents a cross section of cardiac malformations and, indeed, the distribution of anomalies is comparable to those in other studies.[3,4] This study is also unique for its completeness (997 of 1,000 patients) and for the length of follow-up (26 to 37 years). The understanding of the natural history of congenital heart disease is enhanced by our observations.

Several important observations can be made from our study. First, of the 1,000 consecutive patients referred to a pediatric cardiologist, 712 were alive 26 to 37 years after referral. Only 20 have died during the last decade. The survival rate is remarkable, because many of the patients were among the first to undergo open-heart surgery in the United States. The overall operative mortality rate was 15% for the 557 patients undergoing an operation.

Of our patients, 285 died during the period of observation. This mortality rate of 29% does not represent total mortality for congenital heart disease, because it does not include patients who may have died before they were referred to us. Indeed, 446 of the patients were younger than age 1 year at the time of referral, and in this group the mortality was 44%. The number of patients with aortic or pulmonary atresia in our series are in a lower percentage than in other series that have analyzed cardiac disease in infancy.[5,6] However, the 45% infant referral rate is comparable to the data from the Baltimore Washington Infant Study which discusses the proportion of childhood cardiac anomalies evaluated by age 1 year.[7]

Perhaps our mortality rate of 29% on long-term follow-up is similar to that for children currently receiving cardiac care. Although our overall operative mortality is higher than contemporary data, the trend toward earlier referral of severely ill infants and their associated mortality may compensate for this.

In addition, 632 (89%) of our survivors are considered to have excellent or good clinical status, indicating that they are without symptoms or cardiomegaly. However, 80 patients (11%) are symptomatic and several have conditions that are inoperable because of pulmonary vascular obstructive disease; others have undergone an operation but still have symptoms.

The number of specific medical or cardiac complications is low. The occurrence rate of infective endocarditis was 13 of 10,000 patient-years in susceptible patients, and the rate was lower in the last decade. This rate is similar to that reported by other investigators.[8] The occurrence rate was higher in certain conditions (Table III). Endocarditis occurred in patients with the following 5 conditions: tetralogy of Fallot, complete transposition, aortic stenosis, coarctation of the aorta, and VSD defect. Four of the patients died because of endocarditis. We had no instances of endocarditis in patients with either spontaneously or surgically closed VSD.

Brain abscess was uncommon, occurring in 5 of 243 patients with a right-to-left shunt (a rate of 20 per 10,000 patient-years).

Concern has been expressed about the risk of radiation to children with a cardiac malformation, particularly that derived from cardiac catheterization.[9,10] We studied the occurrence of malignancies among our patients and found 6 patients with this condition; only 3 had undergone catheterization. Larger numbers of patients should be studied to determine if a risk exists, but our data do not suggest such an association at this duration of follow-up.

Cardiac rhythm disturbances were relatively uncommon, but we have not studied each patient with continuous electrocardiographic monitoring. A rhythm distur-

bance was described in only 38 patients and, of these, 10 are currently receiving medication. Another 10 of the 38 have a cardiac pacemaker, in most instances for postoperative heart block. Whereas 6 deaths occurred among these 38, it was difficult to attribute the deaths directly to the arrhythmia. Twelve of the 28 without block had 1 or more episodes of recognized and recorded rhythm disturbance, which subsequently reverted to normal or spontaneously disappeared; they do not currently require treatment.

An additional 16 patients are currently receiving a cardiac medication for congestive failure.

Thus, on the basis of this study, we believe that the outlook for children with a cardiac malformation is good. There is, however, 1 group of patients in whom the prognosis must be guarded. In our study, 9 of 62 patients with aortic stenosis have died, 3 suddenly. Furthermore, infective endocarditis occurred in 5 of the 62 (8%). During the past decade, the clinical status of 7 of the 53 survivors with aortic stenosis deteriorated from good to fair, 5 because they required a valve replacement. Certainly, the management of patients with aortic stenosis has posed problems to cardiologists. With the use of echocardiography and balloon valvuloplasty, the outlook for patients with this condition should be improved.

Our data should be helpful to cardiologists who are caring for adults with a congenital cardiac malformation and to those who are discussing with their patients the prognosis of their cardiac malformation.

Acknowledgment: We acknowledge the assistance and skills of June Lewis in locating and contacting many of these patients.

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Diagnosis of Patent Foramen Ovale by Transesophageal Echocardiography and Association with Cerebral and Peripheral Embolic Events

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This study compares the value of transthoracic (TTE) and transesophageal (TEE) color Doppler and contrast echocardiography for detecting a patent foramen ovale (PFO). A total of 238 patients were studied: 74 patients with a history of otherwise unexplained ischemic stroke, transient cerebral ischemic attacks or peripheral embolic events (group A), 48 with a history of similar episodes explained by other cardiac abnormalities (group B), and 116 with no embolic events (group C). A PFO was detected by contrast TEE in 50 of 238 patients (21%) compared with 45 patients (19%) by color Doppler TTE. In a subgroup of 198 patients, TEE results could be compared with TTE findings. No patient had a PFO identified by color Doppler TTE. Contrast TTE detected a PFO in 15 patients (8%) compared with contrast TEE which demonstrated a PFO in 44 of 198 patients (22%) ($p < 0.001$). Prevalence of PFO by TEE was 22, 21 and 22% in groups A, B and C, respectively. A PFO was present in 50% of patients aged <40 years and otherwise unexplained ischemic stroke; this percentage was higher ($p < 0.05$) than corresponding values found in all other groups. Thus, contrast and color Doppler TEE are significantly superior to TTE for detecting PFO. The prevalence of PFO is significantly increased in young adults with otherwise unexplained ischemic stroke.

(Am J Cardiol 1992;70:668–672)

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A patent foramen ovale (PFO) has been reported to be associated with the risk of paradoxical thromboembolism.[1–5] However, the optimal diagnostic approach for identifying a PFO has not been defined. Transthoracic contrast echocardiography (TTE) with venous contrast injection usually has been considered as the noninvasive method of choice for PFO diagnosis.[6–9] Recently, transesophageal echocardiography (TEE) has demonstrated significantly improved ability in detecting interatrial septal defects.[10–12] Accordingly, the present prospective study was designed to compare the value of TTE and TEE contrast and color Doppler echocardiography for detecting PFO. Since PFO has been described as a potential source of arterial embolism, we also analyzed the association between cerebral or peripheral embolism and the presence or absence of PFO.

METHODS

Study patients: The study population consisted of 238 patients (145 men, 93 women) (mean age 52 ± 10 years [range 18 to 84]. Patients were classified into 3 groups.

Group A: This group included 74 patients (45 men, 29 women; age 21 to 69 years) with a history of unexplained ischemic stroke (n = 38), transient cerebral ischemic attacks (n = 27) or peripheral arterial embolic events (n = 9). Diagnosis of suspected cerebral arterial embolism was based on unequivocal acute focal neurologic deficits without other explanation after careful neurologic examination. All patients with stroke and transient ischemic attacks were studied by cerebral computed tomography and 4 patients also underwent magnetic resonance imaging. Nonhemorrhagic infarct zones were demonstrated in all patients with stroke. Computed tomography studies demonstrated cerebral infarct zones in 12 patients after transient ischemic attack and were normal in the other 15 patients. All patients with stroke or transient ischemic attack had undergone carotid Doppler ultrasound examinations; soft plaques were evident in 14 cases. There were no patients with >30% carotid artery obstructions. In patients with peripheral arterial embolism, the diagnosis was confirmed by angiography in all 9 cases. Thromboembolism was substantiated in all 7 of the patients undergoing surgical thrombectomy. In all group A patients, history and cardiovascular physical examination as well as TTE and TEE had not demonstrated any abnormalities (other than PFO) explaining embolism. Patients with

atrial septal aneurysms with or without PFO were also excluded. All patients were in sinus rhythm.

Group B: Forty-eight patients (33 men, 15 women; age 40 to 79 years) had a history of stroke (n = 23), transient ischemic attack (n = 15) or peripheral arterial embolism (n = 10). Diagnoses were documented by computed tomography or magnetic resonance imaging in all patients with stroke and by arteriography in all patients with peripheral arterial embolism (7 of whom had confirmatory surgery). Computed tomography studies showed infarct zones in 8 patients with transient ischemic attacks. However, in these patients, embolic episodes could have been due to the presence of documented mitral valve disease (n = 13), nonvalvular atrial fibrillation (n = 12), dilated cardiomyopathy (n = 9), coronary artery disease (n = 8), aortic valve disease (n = 5) or hypertrophic cardiomyopathy (n = 1). In addition, 16 of these patients showed thrombi in the left atrial appendage (n = 9), left atrium (n = 2) or left ventricle (n = 2), or vegetations on the aortic or mitral valve (n = 3). Furthermore, 4 of the 48 patients revealed protruding atheromas in the thoracic aorta and 2 patients had atrial septal aneurysm.

Group C: In 116 patients (67 men, 49 women; age 18 to 84 years), there was no history of embolic events or neurologic disorders. In 30 of these patients, TEE had been performed because of suboptimal quality of the transthoracic echocardiogram (n = 17) or because of suspected aortic dissection (n = 5), partial anomalous pulmonary venous return (n = 3) or abnormal intra- or extracardiac masses (n = 5). In these 30 patients, TTE and TEE findings were normal (except for presence of PFO). In the remaining 86 patients, the following cardiac disorders were present: mitral valve disease (n = 39), aortic valve disease (n = 31), ischemic heart disease (n = 6), dilated cardiomyopathy (n = 6), dissecting aortic aneuryms (n = 1), patent ductus arteriosus (n = 1), and hypertrophic cardiomyopathy (n = 2).

Echocardiography: TTE studies were performed by standard techniques using 2.5 or 3.5 MHz phased-array transducer systems (Hewlett-Packard Co., Andover, Massachusetts; Acuson Computed Sonography, Mountain View, California). For optimal visualization of the atrial septum, apical 4-chamber and subcostal views were imaged in all patients. TEE studies were performed within 24 hours of the TTE examination with a monoplane (horizontal) 5.0 MHz phased-array transducer attached to the tip of a modified gastroscope (Hewlett-Packard and Acuson Computed Sonography) as described previously.[13,14] Patients had fasted for ≥4 hours and received local pharyngeal anesthesia as the only premedication. All patients gave informed consent and all investigations were performed without complications. TEE examinations were performed exclusively for diagnostic reasons and were usually completed within 5 to 10 minutes.

Contrast echocardiography was performed by injecting 10 ml agitated gelatin solution (Gelifundol®, Biotest Pharma Inc.) rapidly through an antecubital vein. The solution was prepared by shaking the vial and then extruding all macroscopic air. Two to 3 contrast injections were performed during TTE and repeated during all TEE examinations. A Valsalva maneuver was started at the time of contrast injection. When contrast bubbles appeared in the right atrium, the patient was asked to quickly stop straining. A right-to-left shunt was diagnosed when ≥5 microbubbles appeared in the left atrium in the region of the fossa ovalis during the first 3 cardiac cycles after appearance of contrast in the right atrium. A delayed appearance of fine dust-like contrast particles that first entered the left atrium from the pulmonary veins was not considered as being due to PFO. This phenomenon, which could only be visualized by TEE is believed to be due to small amounts of contrast material crossing the pulmonary bed.

PFO was diagnosed by color Doppler echocardiography when a right-to-left shunt through the atrial septum was seen after release of Valsalva maneuver and when no associated permanent left-to-right shunt during normal respiration was present.[15] A low velocity scale was used to detect minimal transseptal gradients.

Only 198 of the 238 patients could be analyzed with regard to presence or absence of PFO by TTE. In 40 patients (12 in group A, 5 in group B, 23 in group C), contrast and color Doppler studies had not been performed (n = 20) or image quality was too poor to allow any evaluation (n = 20).

All TTE and TEE studies were evaluated by 2 independent observers and graded for the presence or absence of a PFO.

Statistical analysis: The Wilcoxon signed rank test was used to compare the diagnostic value of TTE and TEE. For correlation between PFO and the history of embolic events the chi-square test with Yates' correction for small numbers was used. A probability value <0.05 was considered significant.

RESULTS

Comparison between contrast and color Doppler transesophageal echocardiography: A PFO with a right-to-left shunt after Valsalva maneuver was evident by contrast TEE in 50 of the 238 patients (21%) (Fig-

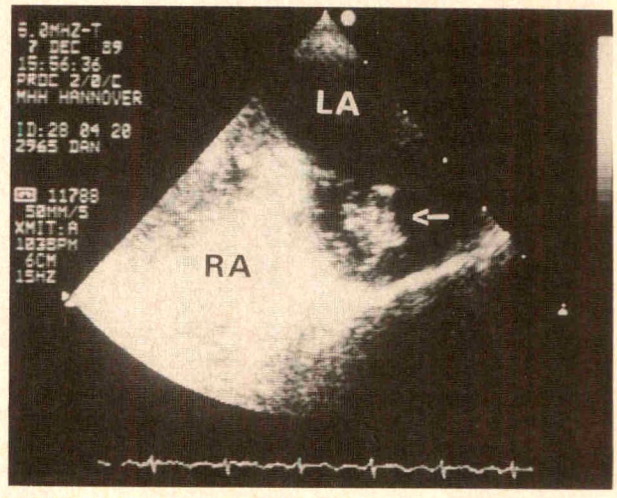


FIGURE 1. Transesophageal contrast echocardiogram in a patient with patent foramen ovale: appearance of echo contrast *(arrow)* on the left atrial (LA) side of the interatrial septum in the region of the foramen ovale after release of Valsalva maneuver. RA = right atrium.

TABLE I Prevalence of a Patent Foramen Ovale in Patients with Unexplained (group A) or Otherwise Explained (group B) Ischemic Cerebral or Arterial Embolic Events and in Patients Without Embolic Events (group C)

	Prevalence of Patent Foramen Ovale		
	Age <40 Years	Age ≥40 Years	All Ages
Group A (n = 74)	9/29 (31%)	7/45 (15.6%)	16/74 (21.6%)
Ischemic stroke	9/18 (50%)	3/20 (15%)	12/38 (31.6%)
Peripheral embolism	0/0 (0%)	2/9 (22.2%)	2/9 (22.2%)
Transient ischemic attack	0/11 (0%)	2/16 (12.5%)	2/27 (7.4%)
Group B (n = 48)	0/4 (0%)	10/44 (22.7%)	10/48 (20.8%)
Ischemic stroke	0/1 (0%)	6/22 (27.3%)	6/23 (26.1%)
Peripheral embolism	0/2 (0%)	1/8 (12.5%)	1/10 (10%)
Transient ischemic attack	0/1 (0%)	3/14 (21.4%)	3/15 (20%)
Group C (n = 116)	2/18 (11.1%)	23/98 (23.5%)	25/116 (21.6%)

Numbers represent numbers of patients (%).

ures 1 and 2). Color Doppler TEE revealed a PFO in 45 patients (19%) (Figures 2 and 3). In 44 patients, a shunt was observed by both techniques, in 6 patients only by contrast and in 1 patient only by color Doppler echocardiography (p = not significant). Evaluation of the 238 TEE studies resulted in an interobserver variability of 2% (5 patients) for the color Doppler and of 1% (2 patients) for the contrast technique.

Comparison between transthoracic and transesophageal echocardiography: In 198 patients, transthoracic echocardiograms could be evaluated for the presence or absence of PFO. Color Doppler TTE did not provide convincing evidence of PFO in any patient. The comparison between TEE and TTE showed a significantly higher detection rate of PFO when using the transesophageal technique: A PFO was found in 44 of the 198 patients (22%) by contrast TEE and in 40 patients (20%) by color Doppler TEE, but in only 15 of the 198 cases (8%) by contrast TTE ($p < 0.001$). There was no patient with positive TTE and negative TEE studies. There was complete interobserver agreement for both contrast and color Doppler TTE.

Association between embolic events and patent foramen ovale: A PFO was regarded as present when documented by either color Doppler or contrast TEE, or both, whether or not confirmed by TTE. The prevalence of PFO in patients in groups A, B and C is listed in Table I. Results are analyzed separately for young patients (<40 years) and older patients (≥40 years). In groups A and B, prevalence of PFO was also analyzed separately for patients with ischemic stroke, transient ischemic attack or peripheral arterial embolism.

In 9 of the 18 patients (50%) aged <40 years with unexplained stroke, a PFO was found. The prevalence of PFO in this subset of patients was significantly higher than that in the remaining patients in group A (chi-square = 4.95; $p < 0.05$), as well as in patients in groups B (chi-square = 4.10; $p < 0.05$), and C (chi-square = 5.24; $p < 0.05$). The characteristics of the 9 patients aged <40 years with otherwise unexplained stroke and

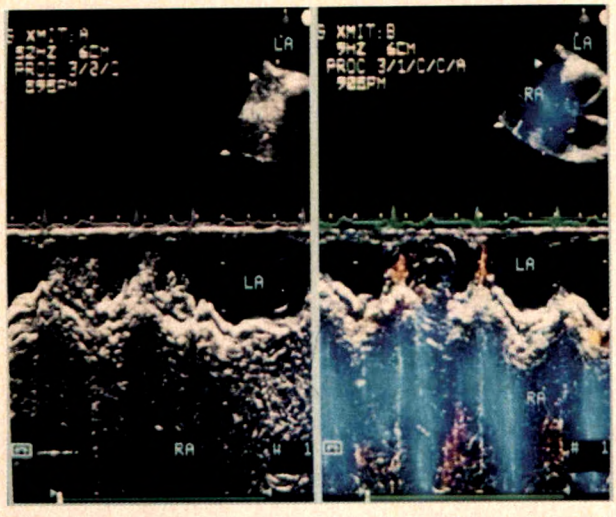


FIGURE 2. Transesophageal echocardiogram in a patient with patent foramen ovale. *Left*, M-mode echocardiogram of the region of the foramen ovale demonstrating contrast shunting from the right (RA) to the left (LA) atrium after release of Valsalva maneuver. *Right*, color Doppler M-mode echocardiogram of the region of the foramen ovale demonstrating a shunt from right atrium to left atrium after release of Valsalva maneuver.

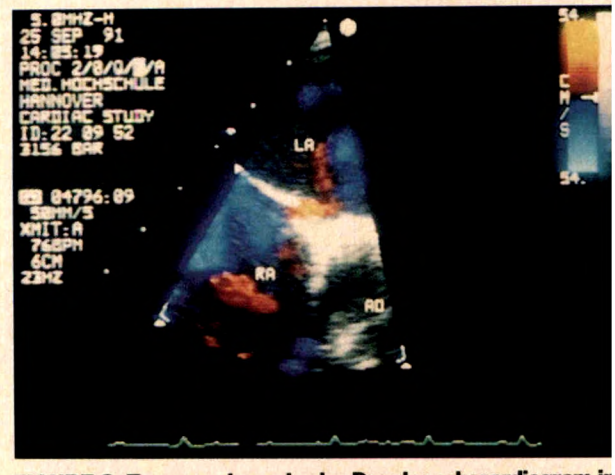


FIGURE 3. Transesophageal color Doppler echocardiogram in a patient with patent foramen ovale: right-to-left shunt through the interatrial septum in the region of the foramen ovale after release of Valsalva maneuver. AO = aorta; LA = left atrium; RA = right atrium.

TABLE II Characteristics of Patients Aged <40 Years with Otherwise Unexplained Ischemic Stroke and Patent Foramen Ovale

Pt. No.	Age (yr) & Sex	Documentation of Stroke	Documentation of PFO			History of Pulmonary Embolism	Venous Status	Further Therapy
			C-TEE	D-TEE	C-TTE			
27	31 M	CT	+	+	0	0	Normal	Aspirin
83	28 F	CT	+	+	0	0	NA	Aspirin
129	37 M	CT	+	+	+	0	CVI	Aspirin
132	30 M	CT	+	+	+	0	DVT	Coumarin
131	38 M	CT	+	+	+	0	CVI	Aspirin
131	38 M	CT	+	+	NA	0	DVT	Coumarin
174	22 M	CT, MRI	+	+	+	0	Normal	Aspirin
233	29 M	CT	+	+	+	0	Normal	Aspirin
238	30 F	CT	+	+	+	+	DVT	Cava filter, coumarin

CT = cranial computed tomography; C-TEE = contrast transesophageal echocardiography; C-TTE = contrast transthoracic echocardiography; CVI = chronic venous insufficiency; D-TEE = color Doppler transesophageal echocardiography; DVT = deep venous thrombosis; MRI = magnetic resonance imaging; NA = not available; PFO = patent foramen ovale.

PFO are listed in Table II. Five of the 9 patients had chronic venous insufficiency by clinical signs or deep venous thrombosis documented by angiography. Also, 1 of the 5 patients had had a mild pulmonary embolism. Except for the latter patient, venous angiograms were recorded after diagnosis of PFO. In the 7 group A patients aged ≥40 years with PFO, venous angiograms were recorded in 5 and deep venous thrombosis could be detected in 1 of them.

DISCUSSION

At autopsy, a PFO is seen in 25 to 30% of cases.[16] The diameter of a PFO may exceed 5 mm,[16] and thrombotic material lodged in a PFO has been documented by autopsy[1,3] and surgery.[2,4,5] Right-to-left shunting through a PFO may occur during coughing or Valsalva maneuver in patients with normal[7,8] or even elevated left atrial pressure.[17]

Diagnosis of patent foramen ovale by echocardiography: PFO is usually diagnosed as an incidental finding in patients undergoing cardiac catheterization. Physical examination and conventional TTE without contrast injection are normal; however, transcranial contrast Doppler ultrasound has been proposed as a diagnostic technique.[18] In patients with PFO, a right-to-left shunt may be detected when contrast echocardiography is performed following Valsalva maneuver or cough.[6–9] However, TTE image quality from an apical 4-chamber or in particular a subcostal view is often impaired during a Valsalva maneuver, and the diagnosis may be missed. In contrast, TEE allows optimal visualization of the atrial septum in virtually all patients under basal conditions and also during Valsalva maneuver or coughing. Furthermore, higher transducer frequencies can be applied leading to a further improvement in image quality.

In the present study, TEE was significantly superior to TTE in detecting a PFO: 8% of patients had a PFO on contrast TTE compared with 22% on contrast TEE. Color Doppler TTE could not identify PFO unequivocally in any patient. This is in contrast to a recently published study by Brickner et al[19] who reported a sensitivity of 90% for PFO diagnosis by color Doppler TTE. In the majority of their PFO patients, however, a permanent left-to-right shunt could be seen, which is very atypical for a PFO with its valve-like morphology. Thus, it cannot be ruled out that at least a few of these patients had a small atrial septal defect instead of a PFO. In our study, contrast and color Doppler TEE showed a nearly comparable yield for detecting PFO. Therefore, both color Doppler and contrast TEE seem to be the methods of choice for detecting PFO.

Clinical relevance of patent foramen ovale: Recently, an association has been described between unexplained cerebral stroke in younger patients and the presence of a PFO. Webster et al[20] detected a PFO by contrast TTE in 20 of 40 patients (50%) aged <40 years with unexplained stroke compared with only 15% of control patients. Using the same technique, Lechat et al[21] observed a PFO in 24 of 60 stroke patients (40%) aged <55 years compared with only 15% found in control subjects. Furthermore, in divers with decompression sickness right-to-left atrial shunting through a PFO has been reported in up to 61%, suggesting that a PFO may be an important component of this disorder.[22]

In the present study, 9 of the 18 patients (50%) aged <40 years with otherwise unexplained ischemic stroke or peripheral arterial embolism had PFO documented by TEE. In patients aged >40 years with unexplained ischemic events, in patients with arterial embolic events explained by other cardiac abnormalities (group B), and in patients without embolism (group C), the prevalence of a PFO was significantly lower. These observations indicate that otherwise unexplained ischemic stroke in younger adults is associated with a significantly higher prevalence of PFO than in other patients or normal subjects.

In the present study, the prevalence of a PFO detected by TEE in patients without arterial embolism or in patients with embolic events potentially due to other cardiac abnormalities was similar to that reported in autopsy studies[16] and in the study of Konstadt et al,[23] which documented a PFO by contrast TEE in 26% of patients during cardiac surgery. These values are higher than the corresponding prevalence of 5 to 18% found in most transthoracic contrast studies in control per-

sons.[6,20–22] The similarity between TEE and autopsy findings is further evidence for the high diagnostic accuracy of the TEE technique.

Several recently published studies have analyzed the value of TTE and TEE for detecting different cardiac sources of arterial embolism, including the presence of a PFO.[24–27] These studies also found that TEE was superior to TTE in detecting PFO.

Study limitations: This study has certain limitations that seem to be unavoidable. First, since a true "gold standard" for demonstrating a PFO during life does not exist, the presence or absence of a PFO could not be proved independently. It is possible that TEE could have missed PFO in some cases[28] and, conversely, some of the results may have been false positive. Second, the control group without embolic events (group C) did not consist of healthy volunteers, because it would be inappropriate to perform TEE in such subjects. Third, arterial embolic events related to a PFO may remain clinically silent. Furthermore, even if an embolic etiology in an individual stroke patient is most likely, a truly definite diagnosis usually cannot be established even if angiography would be performed; also, other reasons for the ischemic cerebral event cannot be ruled out with certainty. Therefore, the true number of patients with embolic events remains unknown. In addition, it is theoretically possible that in some cases embolism was due to an intracardiac mass that had embolized completely and therefore was not detectable by echocardiography. Fourth, the fact that TTE was performed before the TEE examination may be considered as a potential bias improving the accuracy of the TEE evaluation. This bias, however, is unavoidable since TTE should always precede TEE. Fifth, one could argue that the presence of chronic venous insufficiency or deep venous thrombosis in 5 of the 9 stroke patients with PFO and aged <40 years could have biased the echocardiographic diagnosis of PFO. However, this seems to be unlikely since all echocardiograms were read by a second observer unaware of the clinical characteristics, and there was no discrepancy concerning presence or absence of PFO in these cases.

Clinical implications: Our results indicate that the identification of a PFO can be improved significantly by contrast or color Doppler TEE compared with the TTE approach. The increased prevalence of PFO in young adults with otherwise unexplained ischemic stroke indicates an association between the 2 phenomena. The proper management of patients with documented stroke or peripheral embolism and PFO as the only detectable abnormality is not yet defined. In any case, peripheral venous thrombosis should be ruled out. When peripheral venous thrombosis is present, possible therapeutic strategies include closure of the defect by surgery[8,9] or using a transvenous closure device, insertion of an inferior vena cava filter or anticoagulation. Prospective studies addressing these issues are not available.

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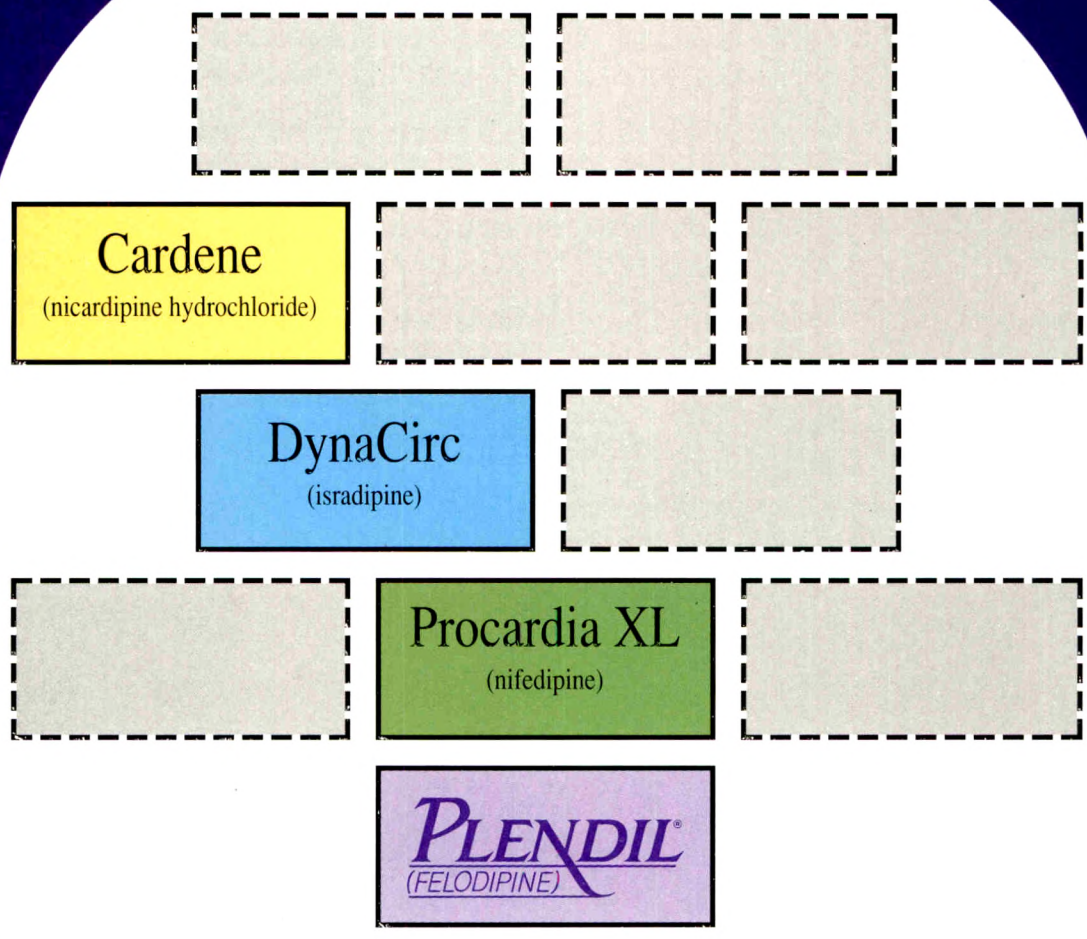
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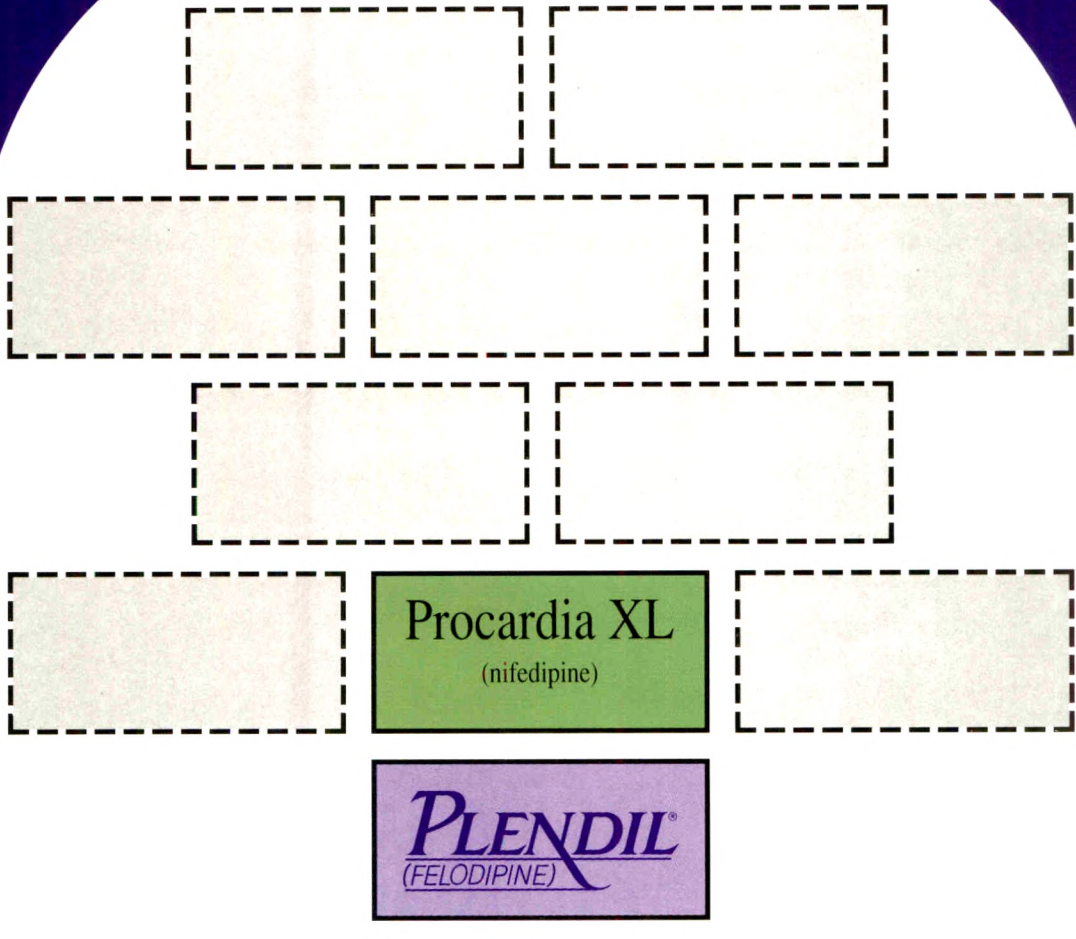
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For hypertension,

These calcium channel blockers are dihydropyridines



Only two dihydropyridine calcium channel blockers offer once-a-day dosing



PLENDIL is...

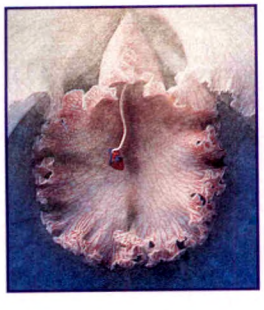
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a dihydropyridine calcium channel blocker that combines...



Tablets not shown actual size.

- **once-a-day dosing**
- **vascular selectivity**
- **savings from 26% to 59% compared with the starting doses of other once-a-day calcium channel blockers***



Once-a-day

PLENDIL®

(FELODIPINE) Tablets, 5 mg 10 mg

For mild-to-moderate hypertension

PLENDIL is contraindicated in patients who are hypersensitive to this product. Felodipine, like other calcium antagonists, may occasionally precipitate significant hypotension and, rarely, syncope. It may lead to reflex tachycardia, which in susceptible individuals may precipitate angina pectoris. (See ADVERSE REACTIONS.)

Although acute hemodynamic studies in a small number of patients with NYHA Class II or III heart failure treated with felodipine have not demonstrated negative inotropic effects, safety in patients with heart failure has not been established. Caution, therefore, should be exercised when using PLENDIL in patients with heart failure or compromised ventricular function, particularly in combination with a beta blocker.

* Based on the usual recommended starting dose(s) from the manufacturers' current product information for once-a-day calcium channel blockers for hypertension. Prices are manufacturers' direct prices, if available, or average wholesale prices from Medi-Span® Prescription Pricing Guide, August 1992, based on the most frequently purchased package size for each strength.

Please see the Brief Summary of Prescribing Information on the last page of this advertisement.

A dihydropyridine calcium channel blocker for mild-to-moderate hypertension

Once-a-day

PLENDIL®

(FELODIPINE)

Available in:



5 mg 10 mg

CONTRAINDICATIONS: PLENDIL is contraindicated in patients who are hypersensitive to this product.

PRECAUTIONS: General: ***Hypotension:*** Felodipine, like other calcium antagonists, may occasionally precipitate significant hypotension and rarely syncope. It may lead to reflex tachycardia which in susceptible individuals may precipitate angina pectoris. (See ADVERSE REACTIONS.)

Heart Failure: Although acute hemodynamic studies in a small number of patients with NYHA Class II or III heart failure treated with felodipine have not demonstrated negative inotropic effects, safety in patients with heart failure has not been established. Caution therefore should be exercised when using PLENDIL in patients with heart failure or compromised ventricular function, particularly in combination with a beta blocker.

Elderly Patients or Patients with Impaired Liver Function: Patients over 65 years of age or patients with impaired liver function may have elevated plasma concentrations of felodipine and may therefore respond to lower doses of PLENDIL. These patients should have their blood pressure monitored closely during dosage adjustment of PLENDIL and should rarely require doses above 10 mg. (See CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION.)

Peripheral Edema: Peripheral edema, generally mild and not associated with generalized fluid retention, was the most common adverse event in the clinical trials. The incidence of peripheral edema was both dose- and age-dependent. Frequency of peripheral edema ranged from about 10 percent in patients under 50 years of age taking 5 mg daily to about 30 percent in those over 60 years of age taking 20 mg daily. This adverse effect generally occurs within 2-3 weeks of the initiation of treatment.

Information for Patients: Patients should be instructed to take PLENDIL whole and not to crush or chew the tablets. They should be told that mild gingival hyperplasia (gum swelling) has been reported. Good dental hygiene decreases its incidence and severity.

NOTE: As with many other drugs, certain advice to patients being treated with PLENDIL is warranted. This information is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects.

Drug Interactions: ***Beta-Blocking Agents:*** A pharmacokinetic study of felodipine in conjunction with metoprolol demonstrated no significant effects on the pharmacokinetics of felodipine. The AUC and C_{max} of metoprolol, however, were increased approximately 31 and 38 percent, respectively. In controlled clinical trials, however, beta-blockers including metoprolol were concurrently administered with felodipine and were well tolerated.

Cimetidine: In healthy subjects pharmacokinetic studies showed an approximately 50 percent increase in the area under the plasma concentration time curve (AUC) as well as the C_{max} of felodipine when given concomitantly with cimetidine. It is anticipated that a clinically significant interaction may occur in some hypertensive patients. Therefore, it is recommended that low doses of PLENDIL be used when given concomitantly with cimetidine.

Digoxin: When given concomitantly with felodipine the peak plasma concentration of digoxin was significantly increased. There was, however, no significant change in the AUC of digoxin.

Other Concomitant Therapy: In healthy subjects there were no clinically significant interactions when felodipine was given concomitantly with indomethacin or spironolactone.

Interaction with Food: See CLINICAL PHARMACOLOGY, *Pharmacokinetics and Metabolism*.

Carcinogenesis, Mutagenesis, Impairment of Fertility: In a two-year carcinogenicity study in rats fed felodipine at doses of 7.7, 23.1 or 69.3 mg/kg/day (up to 28 times* the maximum recommended human dose on a mg/m² basis), a dose-related increase in the incidence of benign interstitial cell tumors of the testes (Leydig cell tumors) was observed in treated male rats. These tumors were not observed in a similar study in mice at doses up to 138.6 mg/kg/day (28* times the maximum recommended human dose on a mg/m² basis). Felodipine, at the doses employed in the two-year rat study, has been shown to lower testicular testosterone and to produce a corresponding increase in serum luteinizing hormone in rats. The Leydig cell tumor development is possibly secondary to these hormonal effects which have not been observed in man.

In this same rat study a dose-related increase in the incidence of focal squamous cell hyperplasia compared to control was observed in the esophageal groove of male and female rats in all dose groups. No other drug-related esophageal or gastric pathology was observed in the rats or with chronic administration in mice and dogs. The latter species, like man, has no anatomical structure comparable to the esophageal groove.

Felodipine was not carcinogenic when fed to mice at doses of up to 138.6 mg/kg/day (28 times* the maximum recommended human dose on a mg/m² basis) for periods of up to 80 weeks in males and 99 weeks in females.

Felodipine did not display any mutagenic activity *in vitro* in the Ames microbial mutagenicity test or in the mouse lymphoma forward mutation assay. No clastogenic potential was seen *in vivo* in the mouse micronucleus test at oral doses up to 2500 mg/kg (506 times* the maximum recommended human dose on a mg/m² basis) or *in vitro* in a human lymphocyte chromosome aberration assay.

A fertility study in which male and female rats were administered doses of 3.8, 9.6 or 26.9 mg/kg/day showed no significant effect of felodipine on reproductive performance.

Pregnancy: ***Pregnancy Category C:*** *Teratogenic Effects:* Studies in pregnant rabbits administered doses of 0.46, 1.2, 2.3 and 4.6 mg/kg/day (from 0.4 to 4 times* the maximum recommended human dose on a mg/m² basis) showed digital anomalies consisting of reduction in size and degree of ossification of the terminal phalanges in the fetuses. The frequency and severity of the changes appeared dose-related and were noted even at the lowest dose. These changes have been shown to occur with other members of the dihydropyridine class and are possibly a result of compromised uterine blood flow. Similar fetal anomalies were not observed in rats given felodipine.

In a teratology study in cynomolgus monkeys no reduction in the size of the terminal phalanges was observed but an abnormal position of the distal phalanges was noted in about 40 percent of the fetuses.

Nonteratogenic Effects: A prolongation of parturition with difficult labor and an increased frequency of fetal and early postnatal deaths were observed in rats administered doses of 9.6 mg/kg/day (4 times* the maximum human dose on a mg/m² basis) and above.

Significant enlargement of the mammary glands in excess of the normal enlargement for pregnant rabbits was found with doses greater than or equal to 1.2 mg/kg/day (equal to the maximum human dose on a mg/m² basis). This effect occurred only in pregnant rabbits and regressed during lactation. Similar changes in the mammary glands were not observed in rats or monkeys.

There are no adequate and well-controlled studies in pregnant women. If felodipine is used during pregnancy, or if the patient becomes pregnant while taking this drug, she should be apprised of the potential hazard to the fetus, possible digital anomalies of the infant, and the potential effects of felodipine on labor and delivery, and on the mammary glands of pregnant females.

Nursing Mothers: It is not known whether this drug is secreted in human milk and because of the potential for serious adverse reactions from felodipine in the infant, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: In controlled studies in the United States and overseas approximately 3000 patients were treated with felodipine as either the extended-release or the immediate-release formulation.

The most common clinical adverse experiences reported with PLENDIL® (Felodipine, MSD) administered as monotherapy in all settings and with all dosage forms of felodipine were peripheral edema and headache. Peripheral edema was generally mild, but it was age- and dose-related and resulted in discontinuation of therapy in about 4 percent of the enrolled patients. Discontinuation of therapy due to any clinical adverse experience occurred in about 9 percent of the patients receiving PLENDIL, principally for peripheral edema, headache, or flushing.

Adverse experiences that occurred with an incidence of 1.5 percent or greater during monotherapy with PLENDIL without regard to causality are compared to placebo in the table below.

Percent of Patients with Adverse Effects in Controlled Trials of PLENDIL as Monotherapy (Incidence of discontinuations shown in parentheses)

Adverse Effect	PLENDIL % N = 730		Placebo % N = 283
Peripheral Edema	22.3	(4.2)	3.5
Headache	18.6	(2.1)	10.6
Flushing	6.4	(1.0)	1.1
Dizziness	5.8	(0.8)	3.2
Upper Respiratory Infection	5.5	(0.1)	1.1
Asthenia	4.7	(0.1)	2.8
Cough	2.9	(0.0)	0.4
Paresthesia	2.5	(0.1)	1.8
Dyspepsia	2.3	(0.0)	1.4
Chest Pain	2.1	(0.1)	1.4
Nausea	1.9	(0.8)	1.1
Muscle Cramps	1.9	(0.0)	1.1
Palpitation	1.8	(0.5)	2.5
Abdominal Pain	1.8	(0.3)	1.1
Constipation	1.6	(0.1)	1.1
Diarrhea	1.6	(0.1)	1.1
Pharyngitis	1.6	(0.0)	0.4
Rhinorrhea	1.6	(0.0)	0.0
Back Pain	1.6	(0.0)	1.1
Rash	1.5	(0.1)	1.1

*Based on patient weight of 50 kg

In the two dose response studies using PLENDIL® (Felodipine, MSD) as monotherapy, the following table describes the incidence (percent) of adverse experiences that were dose-related:

Adverse Effect	Placebo N = 121	5.0 mg N = 72	10.0 mg N = 123	20 mg N =
Peripheral Edema	2.5	13.9	19.5	36.
Palpitation	0.8	0.0	2.4	12.
Headache	12.4	11.1	18.7	28.
Flushing	0.0	2.8	8.1	20.

In addition, adverse experiences that occurred in 0.5 up to 1.5 percent of patients who received PLENDIL in all controlled clinical studies (listed in order of decreasing severity within each category) and serious adverse events that occurred at a lower rate or were found during marketing experience (those lower rate events are in italics) were: *Body as Whole:* Facial edema, warm sensation; *Cardiovascular:* Tachycardia, *myocardial infarction, hypotension, syncope, angina pectoris,* arrhythmia; *Digestive:* Vomiting, dry mouth, flatulence; *Hematologic: Anemia; Musculoskeletal:* Arthralgia, arm pain, knee pain, leg pain, foot pain, hip pain, myalgia; *Nervous/Psychiatric:* Depression, anxiety disorder, insomnia, irritability, nervousness, somnolence; *Respiratory:* Bronchitis, influenza, sinusitis, dyspnea, epistaxis, respiratory infection, sneezing; *Skin:* Contusion, erythema, urticaria; *Urogenital:* Decreased libido, impotence, urinary frequency, urinary urgency, dysuria.

Felodipine, as an immediate release formulation, has also been studied as monotherapy in 680 patients with hypertension in U.S. and overseas controlled clinical studies. Other adverse experiences not listed above and with an incidence of 0.5 percent or greater include: *Body as a Whole:* Fatigue; *Digestive:* Gastrointestinal pain; *Musculoskeletal:* Arthritis, local weakness, neck pain, shoulder pain, ankle pain; *Nervous/Psychiatric:* Tremor; *Respiratory:* Rhinitis; *Skin:* Hyperhidrosis, pruritus; *Special Senses:* Blurred vision, tinnitus; *Urogenital:* Nocturia.

Gingival Hyperplasia: Gingival hyperplasia, usually mild, occurred in <0.5 percent of patients in controlled studies. This condition may be avoided or may regress with improved dental hygiene. (See PRECAUTIONS, *Information for Patients.*)

Clinical Laboratory Test Findings: ***Serum Electrolytes*** No significant effects on serum electrolytes were observed during short- and long-term therapy (see CLINICAL PHARMACOLOGY, *Renal/Endocrine Effects*).

Serum Glucose: No significant effects on fasting serum glucose were observed in patients treated with PLENDIL in the U.S. controlled study.

Liver Enzymes: One of two episodes of elevated serum transaminases decreased once drug was discontinued in clinical studies; no follow-up was available for the other patient.

OVERDOSAGE: Oral doses of 240 mg/kg and 264 mg/kg in male and female mice, respectively, and 2390 mg/kg and 2250 mg/kg in male and female rats, respectively, caused significant lethality.

In a suicide attempt, one patient took 150 mg felodipine together with 15 tablets each of atenolol and spironolactone and 20 tablets of nitrazepam. The patient's blood pressure and heart rate were normal on admission to hospital; he subsequently recovered without significant sequelae.

Overdosage might be expected to cause excessive peripheral vasodilation with marked hypotension and possible bradycardia.

If severe hypotension occurs, symptomatic treatment should be instituted. The patient should be placed supine with the legs elevated. The administration of intravenous fluids may be useful to treat hypotension due to overdosage with calcium antagonists. In case of accompanying bradycardia, atropine (0.5-1 mg) should be administered intravenously. Sympathomimetic drugs may also be given if the physician feels they are warranted.

It has not been established whether felodipine can be removed from the circulation by hemodialysis.

DOSAGE AND ADMINISTRATION: The recommended initial dose is 5 mg once a day. Therapy should be adjusted individually according to patient response, generally at intervals of not less than two weeks. The usual dosage range is 5-10 mg once daily. The maximum recommended daily dose is 20 mg once a day. That dose in clinical trials showed an increased blood pressure response but a large increase in the rate of peripheral edema and other vasodilatory adverse events (see ADVERSE REACTIONS). Modification of the recommended dosage is usually not required in patients with renal impairment.

PLENDIL should be swallowed whole and not crushed or chewed.

Use in the Elderly or Patients with Impaired Liver Function Patients over 65 years of age or patients with impaired liver function, because they may develop higher plasma concentrations of felodipine, should have their blood pressure monitored closely during dosage adjustment (see PRECAUTIONS). In general, doses above 10 mg should not be considered in these patients.

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Hyperventilation Syndrome and the Assessment of Treatment for Functional Cardiac Symptoms

Steven DeGuire, PhD, Richard Gevirtz, PhD,
Yoshito Kawahara, PhD, and William Maguire, MD, PhD

Three methods of breathing retraining (guided breathing retraining, guided breathing retraining with physiologic monitoring of thoracic and abdominal movement plus peripheral temperature, and guided breathing retraining with physiologic monitoring of thoracic and abdominal movement, peripheral temperature and end-tidal carbon dioxide) were compared with a no-treatment control group to determine the effectiveness of breathing retraining on modifying respiratory physiology and reducing functional cardiac symptoms in subjects with signs associated with hyperventilation syndrome. Of 41 subjects studied, 16 were diagnosed with mitral valve prolapse. Results demonstrated that all 3 methods of breathing retraining were equally effective in modifying respiratory physiology and reducing the frequency of functional cardiac symptoms. Results determined that respiratory rate and subject's perception that training had generalized were the best predictors of treatment success. Furthermore, it was found that subjects with mitral valve prolapse responded as well to treatment as did those without prolapse.
(Am J Cardiol 1992;70:673–677)

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It has been estimated that 51 to 90% of all noncardiac-related chest pain is associated with hyperventilation syndrome.[1,2] Recent research also suggests that hyperventilation syndrome may be a major etiologic factor in the pathogenesis of panic disorder.[3–7]

Although there is no generally accepted diagnostic criteria for hyperventilation syndrome, clinical signs of the syndrome are frequently reported to include thoracic, dysrhythmic, rapid and shallow breathing patterns. Frequent yawning and sighing are also frequent.[8–10]

Most researchers believe that chronic episodes of respiratory alkalosis are responsible for the physiologic changes that occur in the syndrome. Evidence has also shown that metabolic compensation occurs in some cases.[11–14] Physiologic changes that occur include dampening of cardiac parasympathetic tone[15] and such electrocardiographic changes as sinus tachycardia, reduction in conduction time, changes in the height of the R wave, and depression of the ST segment.[7,16] Other changes known to occur include a shift to the left in the oxygen disassociation curve, reduced cerebral blood flow,[17] hypophosphatemia,[1] and coronary artery constriction and spasm.[18,19] Symptoms produced frequently include chest pain, arrhythmias, shortness of breath, palpitations, dizziness, tremors, sweating and paresthesia.[20]

Treatment for functional cardiac symptoms generally focuses on the use of several pharmacologic agents. Calcium antagonists, β blockers and nitrates have all been used with varying degrees of success. Patients who are referred for psychiatric consultation are generally administered either tricyclic antidepressant medications or benzodiazepines. Although studies report fairly good success rates with these medications when patients comply with the recommended regime, reported relapse rates are high when medications are withdrawn.[21]

As an alternative to medications, behavioral treatments aimed at restoring normal respiratory physiology and forming new attributions regarding the origin of a patient's symptoms have been used successfully in the treatment of both functional cardiac symptoms and panic disorder.[3,4,8,22–24] Although all these studies have reported high success rates, none have used adequate control groups, and several are based on small numbers of case studies or have been less methodologically rigorous.

Freid[25] proposed that physiologic monitoring of end-tidal carbon dioxide (CO_2)[26] and chest and diaphragmatic movement can contribute to the patient's understanding of how different breathing patterns affect physiology. Given this information, patient's may be more likely to attribute symptoms to the effects of hy-

TABLE I Percentage of Patients Reporting Specific Cardiac Symptoms

Symptom	No. (%)
Chest pain	37 (90)
Palpitation	34 (83)
Shortness of breath	28 (68)
Emotional sweating	23 (57)
Arrhythmias	22 (54)
Tachycardia	19 (46)
Tremors	17 (41)

perventilation. Furthermore, more precise changes in physiology may be achieved by patients who have continuous physiologic information available to them during training.

The current study, in addition to evaluating the effects of breathing retraining on the frequency of functional cardiac symptoms, is designed to evaluate whether physiologic monitoring significantly adds to the treatment of guided breathing retraining.

METHODS

Subjects: Sixty-six subjects (46 women and 20 men, age range 25 to 66 years, mean 42) with functional cardiac symptoms who demonstrated signs of hyperventilation syndrome were referred from physicians offices or responded to an advertisement placed in the classified section of a newspaper. Forty-one subjects completed the study. There was a 37% subject attrition rate which was evenly distributed across all 4 groups. Sixteen subjects who completed the study were diagnosed with mitral valve prolapse.

Subjects had to have been seen by their physician ≤1 year before participation in the study, and all organic causes for cardiac symptoms had to have been ruled out. Patients receiving medications were told not to alter their medication dosage without prior consent from their physician and to notify the experimenter of any change. Cardiac complaints had to occur at least once per week and included chest pain, palpitations, tachycardia and arrhythmias. Subjects frequently reported shortness of breath, tremors and sweating in association with their cardiac complaints. Hence, the frequency and severity of these symptoms were also evaluated. Table I lists the percentage of patients reporting each symptom evaluated in this study before treatment.

Subjects were considered positive for hyperventilation syndrome if they fulfilled any of the following criteria: (1) end-tidal CO_2 ≤36 torr, (2) respiratory rate ≥16, or (3) thoracic breathing. Eight subjects fulfilled 1 criterion, 18 fulfilled 2 criteria, and 15 fulfilled 3 criteria.

Procedure: During the first visit, subjects were interviewed and signed consent forms. Subjects were randomly assigned to 1 of the following 4 groups: (1) guided breathing retraining and physiologic monitoring of diaphragmatic breathing and end-tidal CO_2, (2) guided breathing retraining and physiologic monitoring of diaphragmatic breathing, (3) guided breathing retraining, and (4) no treatment (control). Subjects were unaware that other treatment groups were being evaluated.

Mean end-tidal CO_2 and respiratory rate were recorded using an Ohmeda 5200 CO_2 monitor. Sampling was performed using an aerosol mask with a 1-way valve attached to the intake port and a 15 mm adaptor attached to the exhalation port. The 15 mm adaptor is equipped with a Luer Lock connection to which the gas sampling tube was attached. Although there is generally a slight gradient between end-tidal CO_2 and actual arterial CO_2 pressure, the gradient will only result in significant measurement errors in subjects with low cardiac output, pulmonary disease or increased dead space. Because subjects were screened for any physical abnormalities, the only remaining source of error in measuring CO_2 was dead space. This error can be minimized if only those breaths that show a clear plateau are used to estimate actual arterial CO_2 pressure. This was accomplished by recording the capnograph for ≥2 minutes. In a few cases, a clear plateau could not be obtained. Mode of breathing (thoracic vs diaphragmatic) was recorded using J & J I-330 biofeedback system modules.

Subjects were instructed to record the frequency and severity of symptoms on a standardized log sheet for 2 weeks. Each symptom and symptom episode was rated on a scale from 1 to 9 for severity (symptom recording sheets are available from the authors on request).

Each subject in the 3 treatment groups then attended 6 individualized breathing retraining sessions over a 3-week period. After treatment, subjects again recorded the frequency and severity of cardiac symptoms. Subjects in the control group were instructed to record symptoms for 2 weeks and then to take 3 weeks off, followed by a final 2-week recording period. After post-treatment recording of the frequency and severity of cardiac symptoms, physiologic data were again recorded. Patients also filled out a post-treatment questionnaire. The purpose of the questionnaire was to evaluate any additional benefits subjects thought they had acquired from participating in the study and to determine the extent to which they thought the treatment had generalized. Subjects were asked to estimate the amount of time during the day that they thought they were able to maintain diaphragmatic breathing.

During the first treatment session, subjects in all 3 treatment groups received verbal information concerning respiratory physiology and the hypothesized relation between hyperventilation syndrome and functional cardiac symptoms. Subject's pretreatment physiologic data were reviewed. Subjects were then shown how to breathe diaphragmatically; this was demonstrated by the experimenter. Subjects then practiced diaphragmatic breathing, and any errors were corrected by the experimenter. Discomfort with slow diaphragmatic breathing was frequently reported. Patients were warned and subsequently encouraged to tolerate the discomfort, and were assured that the sensations would abate with time. Although tidal volume measures were not available, patients were carefully observed and encouraged to avoid increased tidal volume as a compensating maneuver for changes in respiratory rate. The focus of the 2 remaining breathing retraining sessions, in addition to correcting errors in diaphragmatic breathing and encouraging a slow-paced respiratory rate (<14

TABLE II Means and Standard Deviations of Pre- Versus Post-treatment Effects on Physiologic and Subjective Measures for Three Breathing Retraining Groups and a Control Group

	Respiratory Rate				End-Tidal CO_2				No. of Days that Symptoms Occurred				Frequency of Cardiac Symptoms			
	$PMETCO_2$	BR	PM	C	$PMETCO_2$	BR	PM	C	$PMETCO_2$	BR	PM	C	$PMETCO_2$	BR	PM	C
Pretreatment																
Mean	15	15	18	15	38	34	34	36	9	8	10	10	23	15	25	27
SD	3	3	3	5	3	3	1	4	5	5	3	4	24	14	23	27
Post-treatment																
Mean	8	9	8	15	41	39	39	36	5	4	5	10	4	9	15	26
SD	3	2	2	5	4	3	4	3	6	5	4	5	21	12	29	26

BR = breathing retraining; C = control; CO_2 = carbon dioxide; PM = physiologic monitoring without end-tidal CO_2; $PMETCO_2$ = physiologic monitoring with end-tidal CO_2.

breaths/min), was to practice diaphragmatic breathing during conversation and during visualization of situations in which subjects felt they were having difficulty maintaining diaphragmatic breathing.

Patients in the breathing retraining group simply repeated the 3 breathing retraining sessions for the final 3 treatment sessions. Criterion was considered fulfilled if patients in this group demonstrated a respiratory rate <14 breaths/min.

For the remaining 3 sessions, patients in the breathing retraining and physiologic monitoring groups were given instructions on the different monitoring devices. Subjects were attached to the thoracic and abdominal strain gauges, and practiced diaphragmatic breathing until they had mastered the technique, as demonstrated by a clear diaphragmatic waveform on the screen.

Subjects who received end-tidal CO_2 monitoring were attached to the CO_2 monitor after they had mastered diaphragmatic breathing. Subjects were encouraged to modify breathing to maximize end-tidal CO_2.

Criteria for patients in the physiologic monitoring without end-tidal CO_2 group were respiratory rate <14 breaths/min and diaphragmatic breathing. Criteria for patients in the physiologic monitoring with end-tidal CO_2 group were the same as for the physiologic monitoring without end-tidal CO_2 group, but also included end-tidal CO_2 >36 torr. All subjects in all 3 treatment groups fulfilled the criteria requirements for their group within the 6 treatment sessions.

RESULTS

Physiologic dependent variables evaluated in this study included respiratory rate and end-tidal CO_2. Subjective dependent variables included the number of days that symptoms occurred, and the total frequency and mean severity of cardiac symptom episodes. Data for each dependent variable were analyzed for homogeneity of variance, normality and presence of outliers. None of the assumptions for analysis of variance were violated. Separate 1-way analysis of variance (ANOVA) tests were calculated for each dependent variable to ensure that there were no pretreatment differences among any of the treatment groups or control group. No pretreatment differences were found. Means and SD for each dependent variable are shown in Table II.

Separate 4 × 2 ANOVAs with 1 repeated measure were performed for each physiologic dependent variable to evaluate the physiologic measures. Because 2 physiologic dependent variables were used to evaluate physiologic change, a Bonferroni correction was used, and a p value <0.017 was needed for the omnibus F tests to be considered significant. In all, 7 additional planned comparisons were obtained for all dependent variables that were found to have a significant time interaction between pre- and post-treatment groups. Because this exceeds the number of planned comparisons that can be obtained without correcting for family-wise error,[27] a modified Bonferroni correction was used. F tests for the planned comparisons were considered significant at p <0.010. Furthermore, the magnitude of treatment effect was calculated for each significant planned comparison and appears in parentheses after the F statements. Power was calculated for each nonsignificant comparison and is expressed in parentheses after the F statement as the number of subjects needed to ensure an 80% probability of finding a treatment effect, if a treatment effect actually exists.

A significant time interaction was found between pre- and post-treatment groups for respiratory rate ($F[3,35] = 14.35$; $p < 0.001$). The simple effects of pre- versus post-treatment respiratory rates were analyzed for each treatment group and the control group; results are as follows: breathing retraining and physiologic monitoring with end-tidal CO_2 monitoring: $F(1,8) = 38.37$, $p < 0.001$ (magnitude of effect = 0.23); breathing retraining and physiologic monitoring without end-tidal CO_2 monitoring: $F(1,8) = 71.57$, $p < 0.001$ (magnitude of effect = 0.39); breathing retraining only: $F(1,8) = 21.52$, $p < 0.001$ (magnitude of effect = 0.18); and control: $F(1,11) = 0.13$, $p = 0.754$. (For the power analysis to fulfill criterion, approximately 4,775 subjects/group would be needed.) A 3 × 2 ANOVA with 1 repeated measure was performed to determine if there was a significant difference between the 3 treatment groups; this analysis did not produce a significant interaction ($F[2,24] = 1.65$; $p = 0.211$). (For the power analysis to fulfill criterion, approximately 125 subjects/group would be needed.)

A significant time interaction was found between pre- and post-treatment groups for end-tidal CO_2. The simple effects of pre- versus post-treatment end-tidal CO_2 were evaluated for each treatment group and the control group; results are as follows: breathing retraining and physiologic monitoring with end-tidal CO_2:

$F(1,8) = 13.52$, $p = 0.006$ (magnitude of effect = 0.12); breathing retraining and physiologic monitoring without end-tidal CO_2: $F(1,8) = 20.87$, $p = 0.002$ (magnitude of effect = 0.27); breathing retraining only: $F(1,8) = 13.84$, $p = 0.006$ (magnitude of effect = 0.12); and control: $F(1,11) = 1.93$, $p = 0.193$. (For the power analysis to fulfill criterion, approximately 275 subjects/group would be needed). A 3 × 2 ANOVA with 1 repeated measure was performed to determine if there was a significant difference between the 3 treatment groups; this analysis did not produce a significant interaction ($F[2, 24] = 0.62$, $p = 0.551$). (For the power analysis to fulfill criterion, approximately 210 subjects/group would be needed.)

Subjective measures were analyzed in the same manner as were physiologic measures. Separate 4 × 2 ANOVAs with 1 repeated measure were performed on each dependent variable. Bonferroni corrections and modified Bonferroni corrections were used to prevent type 1 error.

The 4 × 2 ANOVA with 1 repeated measure for the dependent variable, frequency of cardiac symptom episodes, did not produce a significant time interaction between pre- and post-treatment groups ($F[3,35] = 2.68$; $p = 0.061$). The 3 treatment groups were collapsed into 1 group, and a 2 × 2 ANOVA with 1 repeated measure comparing the combined treatment groups with the control group produced a significant time interaction between pre- and post-treatment groups ($F[1,37] = 8.81$; $p = 0.005$). An analysis of the repeated measure simple effects for the combined treatment groups produced significant differences ($F[1,26] = 27.40$, $p < 0.001$ [magnitude of effect = 0.48]). An analysis of the repeated measure simple effects for the control group did not produce significant differences ($F[1,12] = 0.33$; $p = 0.575$). (For the power analysis to fulfill criterion, approximately 1,200 subjects/group would be needed.)

The 4 × 2 ANOVA with 1 repeated measure for the dependent variable, number of days that symptoms occurred, produced a significant time interaction between pre- and post-treatment groups ($F[3,35] = 4.71$; $p = 0.007$). The simple effects of pre- versus post-treatment number of days that symptoms occurred were evaluated for each treatment group and the control group. The results are as follows: breathing retraining and physiologic monitoring with end-tidal CO_2: $F(1,8) = 7.31$, $p = 0.027$ (magnitude of effect = 0.16); breathing retraining and physiologic monitoring without end-tidal CO_2: $F(1,8) = 24.08$, $p < 0.001$ (magnitude of effect = 0.24); breathing retraining only: $F(1,8) = 10.22$, $p = 0.013$ (magnitude of effect = 0.18); and control: $F(1,11) = 0.14$, $p = 0.713$. (For the power analysis to fulfill criterion, approximately 11,500 subjects/group would be needed.)

The 4 × 2 ANOVA with 1 repeated measure for the dependent variable, mean severity of symptoms, did not produce a significant time interaction between pre- and post-treatment groups ($F[3,55] = 0.33$; $p = 0.809$).

A linear relation was found between several pairs of variables. A reduction in respiratory rate was significantly correlated with a reduction in the frequency of cardiac symptoms ($r = 0.53$; $p < 0.001$) and in the number of days that symptoms occurred, ($r = 0.59$; $p < 0.001$), and an increase in end-tidal CO_2 ($r = 0.38$; $p = 0.018$).

In the post-treatment questionnaire, subjects were asked to estimate the amount of time they could maintain paced diaphragmatic breathing during the course of the day (expressed as percentage of time performing paced diaphragmatic breathing). A linear relation was found between estimated percentage of time performing paced diaphragmatic breathing and several variables. An increase in estimated percentage of time diaphragmatically breathing was correlated with a reduction in the frequency of cardiac symptoms ($r = -0.63$; $p < 0.001$), in the number of days that symptoms occurred ($r = -0.64$; $p < 0.001$) and in respiratory rate ($r = -0.63$; $p < 0.001$), and an increase in end-tidal CO_2 ($r = 0.45$; $p = 0.004$).

An independent rater who was unaware of the purpose of the study evaluated comments that subjects made on the post-treatment questionnaire regarding additional benefits from the study. Although subjects could make any comments they wished, there were 3 main categories of responses. These categories and the number of responses in each were as follows: (1) staying relaxed or in control during stressful situations (n = 14), (2) a general sense of feeling calmer (n = 11), and (3) a sense of well-being or better health (n = 13).

The 3 treatment groups were collapsed to form 1 group, and mitral valve prolapse versus no mitral valve prolapse was introduced as a new independent variable to determine if subjects who were diagnosed with mitral valve prolapse responded differently to treatment. For each dependent variable, 2 × 2 × 2 ANOVAs with 1 repeated measure were then performed. No significant time interactions were found between mitral valve prolapse and treatment groups.

DISCUSSION

This study demonstrated that regardless of the type of breathing retraining a subject received, the frequency of cardiac symptoms decreased after treatment. The most dramatic representation of these results was the reduction in the number of days that symptoms occurred. Furthermore, a reduction in the frequency of cardiac symptoms was accompanied by physiologic changes that included a reduction in respiratory rate and an increase in end-tidal CO_2.

The results obtained for the overall frequency of cardiac symptoms underestimates the actual treatment effect. No measure for duration of symptoms was obtained, and as a result, some patients who had constant chest pain recorded 1 episode of symptoms for the day. After treatment, some of these patients reported mild episodic pain that when recorded appeared as though they had an increase in symptomatology, when in fact they reported feeling improved. Future research should be sensitive to this problem and consider duration of symptoms as a separate dependent variable.

The use of end-tidal CO_2, abdominal and thoracic strain gauge monitors did not add significantly to either reducing the frequency of cardiac symptoms or facilitat-

ing changes in physiology. However, the use of strain gauge monitors produced the largest effect and should be investigated further. Breathing retraining appears to be easily accomplished without the use of sophisticated monitoring equipment. However, the extent to which having concrete physiologic data contributed to the subjects formation of new attributions regarding symptoms is not known. Reviewing pretreatment end-tidal CO_2, breathing mode and respiratory rate with subjects before treatment and then discussing how abnormalities may contribute to cardiac symptomatology may have facilitated the formation of new attributions and increased motivation to participate in treatment.

Two important factors contributing to treatment success are apparent from the results of this study. The first is respiratory rate. There was a strong relation between a reduction in respiratory rate and treatment success. Subjects with the greatest reduction in breathing rate also had the greatest increase in end-tidal CO_2 and the greatest reduction in cardiac symptomatology. Clinically, the observation of reduced respiratory rate may be used as a predictor for treatment success. The second factor contributing to treatment success was the subject's perception that treatment had generalized and that paced diaphragmatic breathing was being maintained. Although it is understood that a subject's perception that they can maintain proper breathing may not accurately reflect their breathing, it is clear from this study that the perception of being able to maintain paced diaphragmatic breathing is a strong predictor for treatment success. Given the ease with which subjects learned paced diaphragmatic breathing, future research should focus on developing techniques that facilitate the generalization of training. Improved research methodology should be used to measure generalization of treatment.

Of further interest in this study was the positive response to treatment that occurred in subjects with mitral valve prolapse. The finding that subjects with mitral valve prolapse respond as well to treatment as do those without mitral valve prolapse suggests that the etiology of symptoms is (at least in part) the same for both groups.

The comments that subjects made on the posttreatment questionnaires suggested that breathing retraining, in addition to reducing cardiac symptoms, is useful in reducing overall anxiety and facilitates a sense of better health and control over one's environment.

It appears apparent from the data that the relations between functional cardiac symptoms and panic disorder is worth further examination. Margraf et al[28] reported that cardiovascular symptoms are reported by nearly all panic patients and are numbered among the most distressing and frequent symptoms.

Acknowledgment: We thank the Ohmeda Company for the use of CO_2 monitoring equipment. We also thank the Biofeedback Institute of San Diego for supporting this study by providing office space and equipment.

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Percutaneous Pericardial Catheter Drainage in Childhood

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The clinical course of 41 consecutive pediatric patients (mean age 7.6 ± 5.8 years, weight 27 ± 22 kg) who underwent percutaneous pericardial drain placement during a 3-year period were reviewed. The most common diagnoses were malignancy (20%), postpericardiotomy syndrome (17%), aseptic pericarditis (12%), and patients recovering from a Fontan type of operation (12%). Indications for drainage included increasing effusion size determined by 2-dimensional echocardiogram (48%), clinical deterioration (33%) and echocardiographic evidence of hemodynamic compromise (12%). Only 3 (7%) patients had clinical evidence of cardiac tamponade.

Drainage catheter placement was accomplished percutaneously from the subxiphoid approach. Insertion was successful in all but 1 patient (98%) and successful evacuation of the pericardial space was achieved in 93% of patients. There was 1 death in a critically ill 2-week-old infant and 4 complications, 3 of which occurred in patients aged <2 years. Drainage catheters remained in position from 1 to 18 days (mean 3 ± 3 days) with no late complications. There were 3 instances (7%) of drainage catheter occlusion. These data support the notion that placement of a percutaneous pericardial catheter is safe and effective in providing definitive drainage of the pericardial space in the pediatric age group. Children younger than age 2 years may be at increased risk for complications.

(Am J Cardiol 1992;70:678–680)

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The technical approach to drainage of hemodynamically significant pericardial effusions continues to be controversial. There have been a number of reports describing the use of indwelling pericardial catheters placed percutaneously at the time of pericardiocentesis in adults[1–5]; however, no large series has addressed the suitability of this procedure in the pediatric population. Over the past 3 years, we have taken the approach that large, clinically significant, nonpurulent pericardial effusions be treated by an indwelling pericardial catheter placed percutaneously at the time of pericardiocentesis. We report this experience with the use of this technique in 41 consecutive pediatric patients.

METHODS

Study patients: The study consisted of 22 male and 19 female patients who underwent percutaneous pericardiocentesis between July 1988 and August 1991. One patient required catheter placement on 3 separate occasions resulting in a total of 43 procedures. Ages ranged from 2 weeks to 16.5 years (mean 7.6 ± 5.8) and weights from 2 to 96 kg (mean 27 ± 22). Data were obtained by retrospective analysis of patient records.

Indications for drainage were: large effusion (n = 21, 49%), defined echocardiographically as a quantity of fluid that could potentially cause hemodynamic embarrassment; hemodynamic compromise (n = 5, 12%), noted echocardiographically as diastolic right atrial or right ventricular collapse; clinical deterioration (n = 14, 32%), assessed as symptoms of tachypnea, dyspnea, tachycardia, restlessness or anxiety when other etiologies could be excluded; and frank evidence of cardiac tamponade (n = 3, 7%) with compromised cardiac output.[6] All patients undergoing pericardiocentesis on the basis of effusion size had effusion diameters measured by echocardiography to be >½ the diameter of the aortic root at the level of the aortic valve closure, corresponding to grades 3 to 5 as defined by Beland et al.[7]

Technique: All procedures were performed under fluoroscopic guidance using standard techniques.[4,5] Use of electrocardiographic monitoring from the aspirating needle (lead V_5) was decided upon by the individual cardiologists. The subxiphoid approach was used in all cases. Observing strict aseptic technique, the skin and subcutaneous tissues were infiltrated with 1% lidocaine, and an 18 gauge needle was introduced at the left xiphocostal margin. Continuous needle aspiration was applied while advancing the needle. Entry into the pericardial space was marked by the appearance of fluid in the syringe. Once within the pericardial space, a 70 cm long, 0.038-inch guidewire (Safe T-J™) was passed

through the needle into the pericardial sac. The needle was removed over the wire and replaced with a vessel dilator (10Fr) which was then replaced with a modified pigtail catheter (8Fr) (Cook Inc., Bloomington, Illinois).[8] The catheter was positioned posteriorly along the lateral border of the heart. The entry site was covered with a dry sterile dressing and the catheter attached to suction (Pleurevac™) at a negative pressure of 10 to 20 cm of water continuously for the duration of the drainage period. Catheters were not routinely flushed with any solutions. All patients underwent 2-dimensional echocardiographic assessment before and within 24 hours of catheter removal.

Statistical analysis: All data are expressed as mean ± 1 standard deviation. A Student's unpaired 2 tailed *t* test was used to examine the relation between catheter duration and quantity of drained fluid. Chi-square analysis was applied when comparing complications within age groups. A p value <0.05 was considered statistically significant.

RESULTS

The etiologies for the effusions are listed in Table I.

Catheter placement: Successful catheter placement was accomplished in 42 of the 43 (98%) attempts. The 1 unsuccessful attempt involved a 6 kg infant who developed acute hemopericardium associated with hypotension during balloon aortic valvuloplasty. Pericardiocentesis drained 25 ml of fresh blood, restoring hemodynamic stability. However, it was not possible to pass a guidewire into the evacuated pericardial space. The patient required no further intervention and recovered without incident.

Fluid appearance: The pericardial fluid was reported as serosanguinous or bloody in 29 cases (67%), serous in 12 (28%) and chylous in 2 (5%).

Duration of indwelling catheter: Catheters remained in the pericardial space for 3 ± 3 days (1 to 18 days). The initial amount drained ranged between 25 and 1,200 ml (mean 320 ± 329) and was not related to patient age, size or diagnosis. Patients requiring an indwelling catheter for >3 days had a significantly greater amount of fluid drained (526 ± 437 ml) at the time of pericardiocentesis than patients needing drainage for <3 days (220 ± 220 ml) ($p = 0.004$). Drainage over the next 48 hours did not differ significantly between groups.

The 1 patient requiring multiple drainage procedures had undergone a modified Fontan operation with creation of an atrial fenestration. Because of recurrent effusions this patient required insertion of a pericardial drain on 2 separate occasions before and once after creation of a pericardial window. Subsequently she was discovered to have a severe stenosis of the left pulmonary artery, which improved after endovascular stent implantation.

Surgical therapy: In 3 cases catheter drainage ceased although 2-dimensional echocardiography demonstrated a persistent effusion. One previously described patient had placement of a second percutaneous drain before surgical creation of a pericardial window. The other 2 patients had surgically created pericardial windows and subsequently recovered uneventfully with no effusion recurrence. One patient with a postoperative persistent chylous effusion required surgical ligation of the thoracic duct.

TABLE I Causes of Pericardial Effusions in 41 Patients

Causes	No. (%)
Malignancy	8 (20)
Postpericardiotomy syndrome	7 (17)
Aseptic pericarditis	5 (12)
Postoperative Fontan	5 (12)
Congestive heart failure	4 (10)
Postoperative complication	4 (10)
Traumatic	3 (7)
Catheterization complication	3 (7)
Connective tissue disease	2 (5)
Total	41 (100)

TABLE II Complications Associated with 43 Percutaneous Pericardial Catheter Procedures

Complication	Age	Weight (kg)
Death	2 weeks	2
Myocardial perforation	3.5 months	4
Myocardial perforation	1 year	7
Pneumopericardium	2 years	11
ST-segment elevation	15 years	38

Complications: There were 4 complications (Table II). All were considered minor, none required specific therapy or interfered with successful catheter placement. There was 1 death which occurred in a critically ill, 14-day-old, 2 kg infant with a complex form of double-outlet right ventricle. Two days earlier the infant had a myocardial perforation during a diagnostic cardiac catheterization requiring surgical repair. During repeat catheterization a large pericardial effusion was noted and during pericardiocentesis a current of injury was noted on the electrocardiogram which was followed by electromechanical dissociation, hypotension and death. Three of the 4 complications and the 1 death occurred in children <2 years of age, with a complication rate of 33% (4 of 12), whereas the complication rate for the 31 procedures performed in children aged >2 years was 3% ($p = 0.006$). There were no late complications.

DISCUSSION

Clinically significant pericardial effusions may complicate the course of children with both cardiac and noncardiac disease. Patients with large effusions are often hemodynamically unstable and in urgent need of therapeutic intervention. Ideally, therapy should consist of a procedure that could be performed quickly with minimal risk and provide immediate symptomatic relief as well as continuous drainage for those patients with ongoing fluid accumulation. Since first described in 1955 by Fallows and Pastor,[1] numerous reports have appeared examining the efficacy and safety of percutaneous catheter drainage in adults.[5,9–12] Whereas there is gathering evidence that this procedure is both safe and effective, particularly when performed under fluoro-

scopic or echocardiographic guidance,[9-12] the debate continues as to whether this method is preferable to surgical drainage. A single report by Lock et al[8] examined this procedure in the pediatric age group. In that study, 7 children were treated with a percutaneously placed pigtail catheter for a duration of 1 to 15 days. Catheter placement was successful in all patients, there were no reported complications, early catheter occlusion was common (3 of 7), and 3 of the patients were aged <2 years.

Percutaneous catheter insertion in this study was accomplished in 98% of patients, comparing favorably with the most recent series in adults[10] in which successful placement occurred in 42 of 46 patients (91%). Similarly, the number of patients whose effusions were successfully treated with this technique alone (38 of 41, 93%) compared favorably with the published series on adults in which success rates ranged from 76 to 98%.[10,11] The small number of children requiring eventual surgical drainage of the pericardial space or repeated catheter insertion suggests that this method provides definitive therapy in most cases. No patient had a clinical presentation consistent with a purulent pericarditis. Our usual policy is to have these patients undergo diagnostic pericardiocentesis, but the preferred treatment is open surgical drainage and creation of a pericardial window.[13] However, little or no information exists defining the best approach to this situation in childhood.

It appears from the data that the amount of fluid drained related to the duration of catheter implantation. However, there was considerable overlap between the 2 groups (i.e., those needing the drainage catheter in place <3 days versus >3 days).

Pericardiocentesis has been reported to be more difficult and associated with a higher morbidity in children than in adults.[14,15] Whereas in this study the safety of the procedure in children aged >2 years is acceptable (3% complication rate), the group aged <2 years would appear to be at increased risk for developing a procedure-related complication. This could relate to their small size (average weight 8.8 vs 33.8 kg), the small quantity of fluid resulting in clinically significant effusions, and the close proximity of pertinent anatomic structures. Within that group <2 years old, the mean weight was 6 kg, compared to 10 kg in those who were free from complications. With the assistance of 2-dimensional echocardiography to better localize the effusion and guide the trajectory of the needle,[9,11,12] the risks in this age group could be reduced. The use of smaller Teflon™ sheath needles, thinner guidewires, and softer, smaller catheters in the younger children may also lessen morbidity and mortality. It has been suggested that intermittent drainage decreases the incidence of catheter occlusion[11] when compared with continuous drainage; however, in this series all patients had continuous drainage, making an examination of this variable impossible.

Many patients in the current series had electrocardiographic lead V_5 monitoring through the aspirating needle. We found this technique unhelpful and at times cumbersome. A myocardial injury current was noted only in the 1 patient who died and in that particular instance the presence of an injury potential did not alter the final outcome. In all other cases, entry into the pericardial space was marked by the appearance of fluid in the aspirating syringe. With fluoroscopic or perhaps echocardiographic guidance the need for such electrocardiographic monitoring is questionable.

Conclusion: This study demonstrates that the technique of percutaneous pericardial drainage is safe and efficacious in draining clinically significant pericardial effusions in the pediatric age group. There appears to be some increased risk when the procedure is performed in small infants.

Study limitations: Although this study consists of an unselected consecutive series of patients with nonpurulent pericardial effusions requiring pericardial drainage, it is retrospective in nature and reflects the experience of a large tertiary care center seeing a large number of pediatric cardiac patients. As with any invasive technique, experience and familiarity will influence results.

Finally, a large effusion was the indication for drainage in nearly ½ of the patients. The absolute size of an effusion has not been shown to correlate well with hemodynamic compromise in adults.[16] A recent report suggests that in children, an effusion ≥¾ the diameter of the aortic root places them at increased risk of developing cardiovascular compromise.[7] Further study is needed before recommendations can be made as to the size of effusion requiring intervention.

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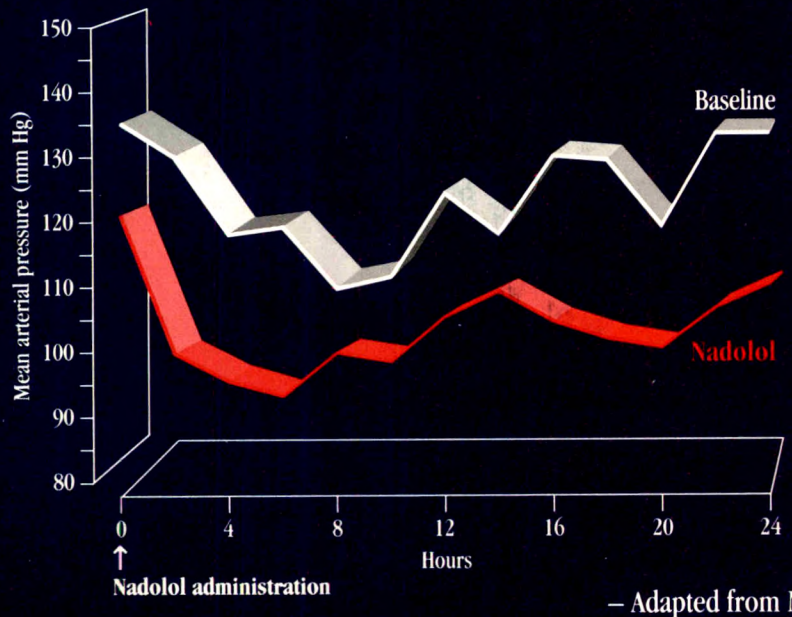
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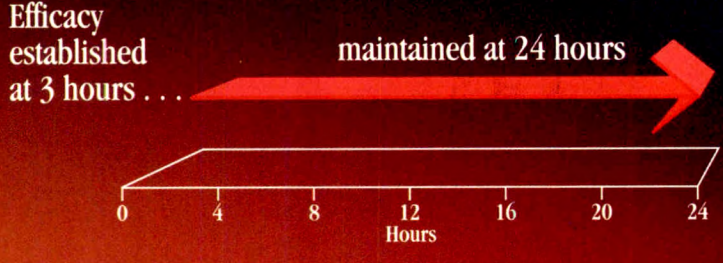
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True Sunrise-to-sunrise control

Please see brief summary of prescribing information on adjacent page.

CORGARD® TABLETS
Nadolol Tablets USP

DESCRIPTION: CORGARD (nadolol) is a synthetic nonselective beta-adrenergic receptor blocking agent.

CONTRAINDICATIONS: Bronchial asthma, sinus bradycardia and greater than first degree conduction block, cardiogenic shock, and overt cardiac failure (see WARNINGS).

WARNINGS: Cardiac Failure–Sympathetic stimulation may be a vital component supporting circulatory function in congestive heart failure, and its inhibition by beta-blockade may precipitate more severe failure. Although beta-blockers should be avoided in overt congestive heart failure, if necessary, they can be used with caution in patients with a history of failure who are well compensated, usually with digitalis and diuretics. Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle. IN PATIENTS WITHOUT A HISTORY OF HEART FAILURE, continued use of beta-blockers can, in some cases, lead to cardiac failure; therefore, at first sign or symptom of heart failure, digitalize and/or give diuretics, and closely observe response, or discontinue nadolol (gradually if possible).

Exacerbation of Ischemic Heart Disease Following Abrupt Withdrawal–Hypersensitivity to catecholamines has been observed in patients withdrawn from beta-blocker therapy; exacerbation of angina and, in some cases, myocardial infarction have occurred after *abrupt* discontinuation of such therapy. When discontinuing chronic use of nadolol, particularly in patients with ischemic heart disease, gradually reduce dosage over a 1- to 2-week period and carefully monitor the patient. Reinstitute nadolol promptly (at least temporarily) and take other measures appropriate for management of unstable angina if angina markedly worsens or acute coronary insufficiency develops. Warn patients not to interrupt or discontinue therapy without physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue nadolol therapy abruptly even in patients treated only for hypertension.

Nonallergic Bronchospasm (eg, chronic bronchitis, emphysema)–PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA-BLOCKERS. Administer nadolol with caution since it may block bronchodilation produced by endogenous or exogenous catecholamine stimulation of β_2 receptors.

Major Surgery–Because beta-blockade impairs the ability of the heart to respond to reflex stimuli and may increase risks of general anesthesia and surgical procedures, resulting in protracted hypotension or low cardiac output, it has generally been suggested that such therapy should be withdrawn several days prior to surgery. Recognition of the increased sensitivity to catecholamines of patients recently withdrawn from beta-blocker therapy, however, has made this recommendation controversial. If possible, withdraw beta-blockers well before surgery takes place. In emergency surgery, inform the anesthesiologist that the patient is on beta-blocker therapy. Use of beta-receptor agonists such as isoproterenol, dopamine, dobutamine, or levarterenol can reverse the effects of nadolol. Difficulty in restarting and maintaining the heartbeat has also been reported with beta-adrenergic receptor blocking agents.

Diabetes and Hypoglycemia–Beta-adrenergic blockade may prevent the appearance of premonitory signs and symptoms (eg, tachycardia and blood pressure changes) of acute hypoglycemia. This is especially important with labile diabetics. Beta-blockade also reduces release of insulin in response to hyperglycemia; therefore, it may be necessary to adjust dose of antidiabetic drugs.

Thyrotoxicosis–Beta-adrenergic blockade may mask certain clinical signs (eg, tachycardia) of hyperthyroidism. To avoid abrupt withdrawal of beta-adrenergic blockade which might precipitate a thyroid storm, carefully manage patients suspected of developing thyrotoxicosis.

PRECAUTIONS: Impaired Renal Function–Use nadolol with caution (see DOSAGE AND ADMINISTRATION section of package insert).

Information for Patients–Warn patients, especially those with evidence of coronary artery insufficiency, against interruption or discontinuation of nadolol without physician's advice. Although cardiac failure rarely occurs in properly selected patients, advise patients being treated with beta-adrenergic blocking agents to consult physician at first sign of impending failure. Advise patients in event of missed doses.

Drug Interactions–Concurrent administration may result in interactions with: Anesthetics, general—exaggeration of the hypotension induced by general anesthetics (see WARNINGS, Major Surgery). Antidiabetic drugs (oral agents and insulin)–hypoglycemia or hyperglycemia; adjust antidiabetic drug dosage accordingly (see WARNINGS, Diabetes and Hypoglycemia). Catecholamine-depleting drugs (eg, reserpine)–additive effect; monitor closely for hypotension and/or excessive bradycardia.

Response to Treatment for Anaphylactic Reaction–While taking beta-blockers, patients with a history of severe anaphylactic reaction to a variety of allergens may be more reactive to repeated challenge, either accidental, diagnostic, or therapeutic. Such patients may be unresponsive to the usual doses of epinephrine used to treat allergic reaction.

Carcinogenesis, Mutagenesis, Impairment of Fertility–In 1- to 2-year oral toxicologic studies in mice, rats, and dogs, nadolol did not produce significant toxic effects. In 2-year oral carcinogenic studies in rats and mice, nadolol did not produce neoplastic, preneoplastic, or nonneoplastic pathologic lesions.

Pregnancy Category C–In animal reproduction studies with nadolol, evidence of embryo- and fetotoxicity was found in rabbits (but not in rats or hamsters) at doses 5 to 10 times greater (on a mg/kg basis) than maximum indicated human dose; no teratogenic potential was seen in any of these species. There are no well-controlled studies in pregnant women; therefore, use nadolol in pregnant women only if potential benefit justifies potential risk to the fetus. Neonates of mothers who received nadolol at parturition have exhibited bradycardia, hypoglycemia, and associated symptoms.

Nursing Mothers–Nadolol is excreted in human milk. Exercise caution when nadolol is administered to a nursing woman.

Pediatric Use–Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: Most adverse effects have been mild and transient and have rarely required nadolol withdrawal.

Cardiovascular–Bradycardia with heart rates of less than 60 beats per minute occurs commonly, and heart rates below 40 beats per minute and/or symptomatic bradycardia were seen in about 2 of 100 patients. Symptoms of peripheral vascular insufficiency, usually of the Raynaud type, have occurred in approximately 2 of 100 patients. Cardiac failure, hypotension, and rhythm/conduction disturbances have each occurred in about 1 of 100 patients. Single instances of first degree and third degree heart block have been reported; intensification of AV block is a known effect of beta-blockers (see also CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS). **Central Nervous System**–Dizziness or fatigue reported in approximately 2 of 100 patients; paresthesias, sedation, and change in behavior reported in approximately 6 of 1000 patients. **Respiratory**–Bronchospasm reported in approximately 1 of 1000 patients (see CONTRAINDICATIONS and WARNINGS). **Gastrointestinal**–Nausea, diarrhea, abdominal discomfort, constipation, vomiting, indigestion, anorexia, bloating, and flatulence each reported in 1 to 5 of 1000 patients. **Miscellaneous**–Each of the following reported in 1 to 5 of 1000 patients: rash; pruritus; headache; dry mouth, eyes, or skin; impotence or decreased libido; facial swelling; weight gain; slurred speech; cough; nasal stuffiness; sweating; tinnitus; blurred vision; infrequent reversible alopecia.

The following adverse reactions have been reported in patients taking nadolol and/or other beta-adrenergic blocking agents, but no causal relationship to nadolol has been established. **Central Nervous System**–reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place; short-term memory loss, emotional lability with slightly clouded sensorium; decreased performance onneuropsychometrics. **Gastrointestinal**–mesenteric arterial thrombosis; ischemic colitis; elevated liver enzymes. **Hematologic**–agranulocytosis;thrombocytopenic or nonthrombocytopenic purpura. **Allergic**–fever combined with aching and sore throat; laryngospasm; respiratory distress. **Miscellaneous**–pemphigoid rash; hypertensive reaction in patients with pheochromocytoma; sleep disturbances; Peyronie's disease. The oculomucocutaneous syndrome associated with practolol has not been reported with nadolol.

OVERDOSAGE: Nadolol can be removed from the general circulation by hemodialysis. In addition to gastric lavage, employ the following measures as appropriate. In determining duration of corrective therapy, take note of long duration of effect of nadolol.

Excessive Bradycardia–Administer atropine (0.25 to 1.0 mg). If there is no response to vagal blockade, administer isoproterenol cautiously.

Cardiac Failure–Administer a digitalis glycoside and diuretic. It has been reported that glucagon may also be useful in this situation.

Hypotension–Administer vasopressors, eg, epinephrine or levarterenol. (There is evidence that epinephrine may be the drug of choice.)

Bronchospasm–Administer a β_2-stimulating agent and/or a theophylline derivative.

DOSAGE–For all patients, DOSAGE MUST BE INDIVIDUALIZED.

For **angina pectoris**, usual initial dose is 40 mg qd; may be gradually increased in 40 to 80 mg increments at 3 to 7 day intervals until optimum clinical response or pronounced slowing of the heart rate; usual maintenance dose is 40 or 80 mg qd (doses up to 160 or 240 mg daily may be needed). If treatment is to be discontinued, reduce dosage gradually over a period of 1 to 2 weeks (see WARNINGS).

For **hypertension**, usual initial dose is 40 mg qd; gradually increase in 40 to 80 mg increments until optimum blood pressure reduction is achieved; usual maintenance dose is 40 or 80 mg qd (doses up to 240 or 320 mg daily may be needed).

Patients with renal failure require adjustment in dosing interval; see package insert for dosage in these patients.

For full prescribing information consult package insert.

HOW SUPPLIED: In scored tablets containing 20, 40, 80, 120, or 160 mg nadolol per tablet in bottles of 100. The 40 mg, 80 mg, and 120 mg tablets are available in bottles of 1000 tablets. The 20 mg, 40 mg, and 80 mg tablets are also available in Unimatic® unit-dose packs of 100 tablets.

CORGARD® (nadolol) 40 mg tablets



Sunrise-to-sunrise control in hypertension and angina pectoris

Convenient once-daily dosing



20 mg 40 mg 80 mg

Also available in 120 mg and 160 mg tablets

References:
1. Mancia G, Ferrari A, Pomidossi G, et al. Twenty-four-hour hemodynamic profile during treatment of essential hypertension by once-a-day nadolol. *Hypertension.* 1983;5:573-578.
2. Kostis JB, Lacy CR, Krieger SD, Cosgrove NM. Atenolol, nadolol, and pindolol in angina pectoris on effort: effect of pharmacokinetics. *Am Heart J.* 1984;108:1131-1136.

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B-K81-1-92

A New Classification of Left Ventricular Geometry in Patients with Cardiac Disease Based on M-Mode Echocardiography

Farhad U. Huwez, PhD, Stuart D. Pringle, MD, and Peter W. Macfarlane, PhD

M-mode echocardiograms of 202 cardiac patients were studied with respect to the pattern of left ventricular (LV) geometry. Patients with normal LV mass and volume were separated from those who had LV hypertrophy or enlargement on the basis of LV mass and volume indexed to body surface area. The relative wall thickness that is currently used to classify LV hypertrophy/enlargement was found to be inadequate for differentiating between concentric and eccentric types of LV hypertrophy. A new M-mode echocardiographic classification is therefore proposed that accurately separates the different types of LV enlargement; it also allows identification of patients who have chronically dilated left ventricles at the expense of thin walls and thus have normal LV mass.

(Am J Cardiol 1992;70:681–688)

Concentric left ventricular (LV) hypertrophy occurs in response to pressure overload where there is a marked increase in wall thickness but no increase in LV cavity size. In eccentric LV hypertrophy, the LV dilatation due to volume overload is more significant than the increase in the LV wall thickness.[1–6] In the Framingham Study,[7] echocardiographically diagnosed LV hypertrophy was classified into concentric and eccentric types by using a cutoff point of the relative wall thickness so that a value ≥45% was used to indicate concentric and a value <45% suggested eccentric LV hypertrophy. Eccentric LV hypertrophy was further subclassified into dilated and nondilated types according to the LV internal dimension at end-diastole (indexed to sex and body surface area).

Nondilated eccentric LV hypertrophy was the most common type of LV hypertrophy in that study.[7] Patients in this group had increased indexed LV mass, a relative wall thickness <45% and, by definition, normal indexed LV internal dimension at end-diastole, which in effect means a normal LV volume since this is derived from the cube of the LV internal dimension at end-diastole. However, an increased LV volume is the stimulus for the development of eccentric LV hypertrophy.[1] Therefore, there is a conflict in that nondilated eccentric LV hypertrophy is a dubious entity. Furthermore, it is not clear how relative wall thickness can differentiate among the various types of LV enlargement when LV volumes and masses are used as the gold standard; this is especially true in a sample of the cardiac population where a wide variety of LV geometry is expected. For these reasons, it was decided to study a group of cardiac patients to examine, in detail, methods of classifying LV geometry into normal and abnormal, with the latter being subdivided into various groups.

METHODS

Patients: Consecutive cardiac patients undergoing echocardiography for investigation of cardiovascular disease were studied. The echocardiograms were recorded with a Diasonics Cardiovue 3400 phased-array imaging system using a 2.25 MHz transducer. However, only patients with good echocardiographic recordings were included so that 117 patients had to be excluded for technical reasons. In addition, patients with hypertrophic obstructive cardiomyopathy were also excluded from the study.

Patients were positioned semisupine in the 45° left lateral position, and the echo windows that best demonstrated the septal and posterior wall were chosen in the third, fourth or fifth intercostal space in the left parasternal area. Two-dimensionally directed M-mode re-

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TABLE I Distribution of the Underlying Pathologic States in 202 Patients Included in the Study

Pathologic State	No. of Pts.
Systemic hypertension	61
Aortic stenosis and/or incompetence	43
Mitral stenosis and/or incompetence	31
Mixed mitral (stenosis and/or incompetence) with aortic stenosis and/or incompetence	16
Aortic valve and coronary artery disease	8
Coronary artery disease	5
Myocardial infarction	11
Congestive cardiac failure	11
Miscellaneous	16
Total	202

cordings were obtained and the interventricular septum, posterior wall of the left ventricle and LV internal dimension at end-diastole were measured by using both the recommendations of the American Society of Echocardiographers[8] and the Penn convention[9] (Figure 1). All measurements were obtained to the nearest millimeter. The following equations were used for the calculation of the relative wall thickness,[7] LV masses[9,10] and volume[11]:

$$\text{Relative wall thickness} = \frac{2 \times \text{PWLV}}{\text{LVIDD}} \times 100\%$$

$$\text{LV volume} = \frac{3.14 \times \text{LVIDD}^3}{3}\ \text{cm}^3$$

where LVIDD = LV internal dimension at end-diastole, and PWLV = posterior wall thickness of the left ventricle, measured according to the recommendations of the American Society of Echocardiographers; and LV mass (Penn) = 1.04 {(VS + PWLV + LVIDD)^3 − (LVIDD)^3}−13.6g where all measurements were obtained according to the Penn convention.[9] In this case, VS = thickness of intraventricular septum.

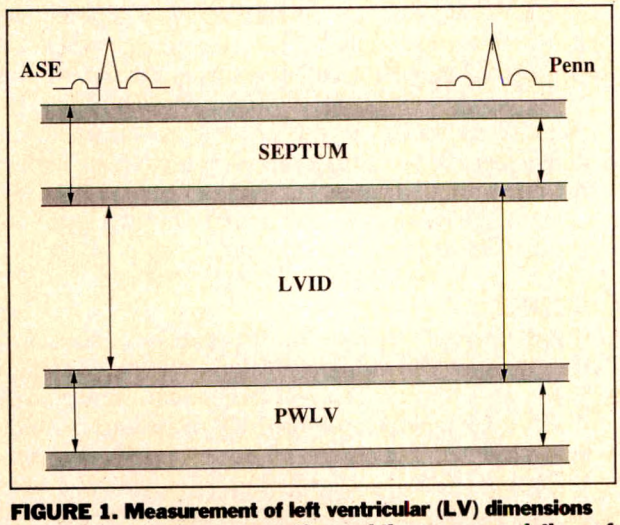


FIGURE 1. Measurement of left ventricular (LV) dimensions according to the Penn convention and the recommendations of the American Society of Echocardiographers (ASE). According to the Penn convention, the endocardial echos are excluded from the measurements of the interventricular septum and posterior wall of the left ventricle (PWLV), but are included in the measurements of left ventricular internal dimensions (LVID). American Society of Echocardiographers measurements include endocardial echos in the interventricular septum and posterior wall of the left ventricle. (Reproduced with permission of *Int J Cardiol.*)

Echocardiographically, LV mass has been reliably indexed to sex and body surface area by using the Penn convention.[12] In the present study, echo measurements obtained in the same subjects according to the American Society of Echocardiographers recommendations were used for calculation of LV volumes and relative wall thickness because normal values of LV volumes[11] and evaluation of relative wall thickness for classification of LV hypertrophy[7] by echocardiography has until now been based on such recommendations. LV volumes and masses of all the subjects were indexed to body surface area (BSA) which was calculated from the following equation[13]: BSA (m^2) = (0.0001) × (71.84) × ($wt^{0.425}$) × ($ht^{0.725}$) where body surface area is in m^2, weight (wt) in kg and height (ht) in cm.

LV hypertrophy was diagnosed when the indexed LV mass (Penn) exceeded 131 g/m^2 in men and 108 g/m^2 in women.[12] Thereafter, patients with LV hypertrophy were classified into concentric and eccentric types on the basis of their relative wall thickness ≥45 or <45%, respectively, as previously explained. Indexed LV volumes were studied in both concentric and eccentric LV hypertrophy. LV dilatation was diagnosed when LV volume exceeded 90 ml/m^2.[11]

RESULTS

Clinical data: Two hundred two cardiac patients (116 men and 86 women, mean age 52.12 years [range 16 to 87]) were included in the study. The underlying pathologic conditions of these patients are listed in Table I.

Echocardiographic measurements: The mean ± standard deviation and ranges of LV dimensions from both the American Society of Echocardiographers and Penn conventions are listed in Table II. There were statistically significant differences ($p < 0.001$) between all LV dimensions measured according to both the American Society of Echocardiographers and Penn conventions (paired *t* tests). The mean ± standard deviation and range of estimated indexed LV mass and volume are listed in Table II. There were highly significant differences ($p < 0.001$) between the masses and volumes obtained from the 2 different conventions (paired *t* test). One hundred thirty-eight of the 202 subjects (68%) in this cardiac population had LV hypertrophy (Figure 2). Severe LV hypertrophy (indexed mass >200 g/m^2) was found in 52 of the 138 patients (37%) with LV hypertrophy.

Classification of left ventricular hypertrophy/enlargement by relative wall thickness: Patients with LV hypertrophy were classified on the basis of their relative wall thickness into concentric (relative wall thickness ≥45%) and eccentric (relative wall thickness <45%) types. As a result of this classification, 56 patients (33%) had concentric and 82 (67%) had eccentric LV hypertrophy. Indexed LV volume and relative wall

TABLE II Mean ± Standard Deviation and Range of Left Ventricular Dimensions and Indexed Left Ventricular Mass and Volume According to Recommendations of the American Society of Echocardiographers and the Penn Convention for the 202 Patients in the Study*

Echo Convention	Ventricular Septum (cm)	LV Posterior Wall Thickness (cm)	LV Internal Diastolic Dimension (cm)	LV Volume (ml/m^2)	LV Mass (g/m^2)
ASE					
mean ± SD	1.3 ± 0.4	1.2 ± 0.3	5.2 ± 1.0	94 ± 55	193 ± 82
range	0.5 → 2.7	0.5 → 2.7	2.9 → 8.2	16 → 325	71 → 532
PENN					
mean ± SD	1.1 ± 0.4	1.1 ± 0.3	5.4 ± 1.0	105 ± 61	165 ± 75.5
range	0.4 → 2.5	0.4 → 2.6	3.1 → 8.4	19 → 362	64 → 505

*There were significant differences ($p < 0.001$) between all dimensions using the different convention measurements.
ASE = American Society of Echocardiographers; Echo = echocardiography; LV = left ventricular; PENN = Penn convention.

thickness correlated well ($r = -0.85778$) in the population with LV hypertrophy. However, 10 of 56 patients (18%) with concentric LV hypertrophy had LV volume >90 ml/m^2 (i.e., a dilated left ventricle [Figure 3]), whereas 20 of 82 patients (24%) with eccentric LV hypertrophy had LV volume <90 ml/m^2 (Figure 4). Therefore, classification of LV hypertrophy on the basis of relative wall thickness in this cardiac population produced one sub-group of patients with concentric LV hypertrophy and dilated ventricles and another sub-group of patients with eccentric LV hypertrophy and normal LV volume.

Classification of left ventricular hypertrophy/enlargement by mass/volume relation: Because the classification of LV hypertrophy on the basis of relative wall thickness produced inconsistencies mentioned previously, a new approach was adopted for classifying patients in this study on the basis of LV mass and volume. This allowed identification of four distinct groups (Table III). On the basis of this classification, a small group of patients were identified who had increased LV volume but normal LV mass (isolated LV volume overload) (Figure 5). The differences between the Framingham classification[7] and the newly proposed approach to

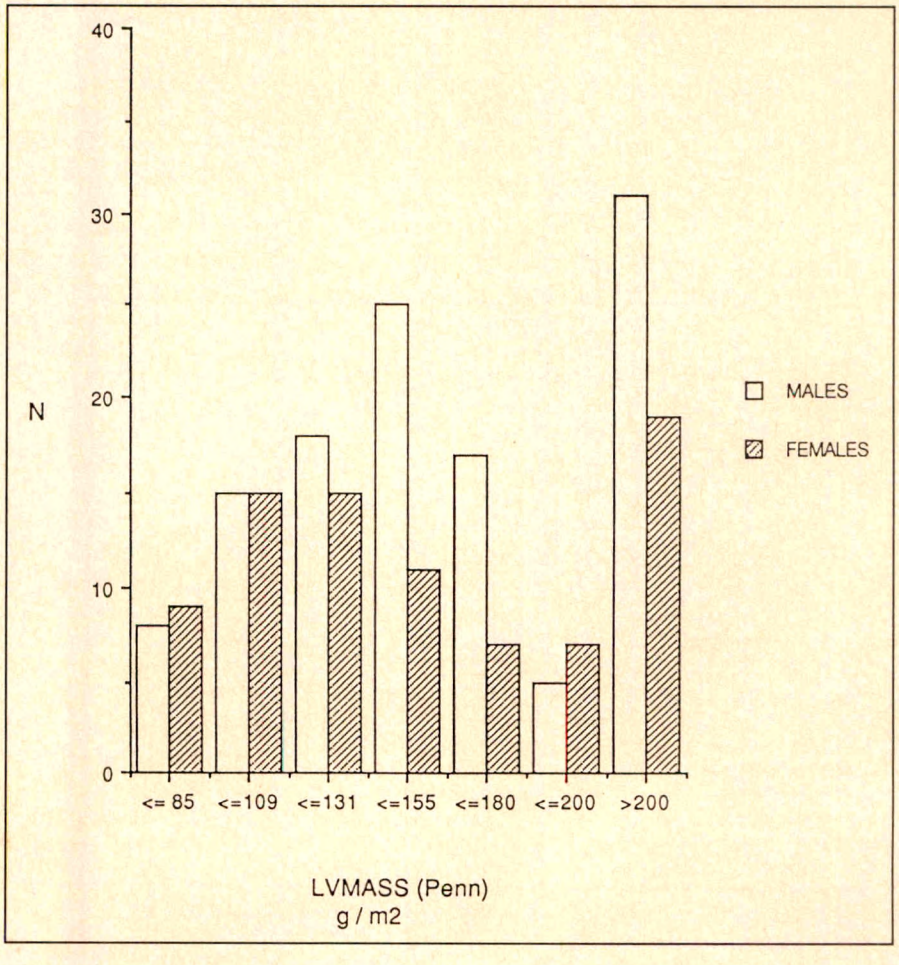


FIGURE 2. Distribution of the indexed left ventricular (LV) masses in g/m^2 from the measurements of the Penn convention for 202 men and women included in the study.

echocardiographic classification for LV hypertrophy/enlargement are shown schematically in Figures 6 and 7, respectively. The mean ± standard deviation and range of indexed LV mass (Penn) and LV volume (American Society of Echocardiographers) of the 4 newly proposed groups are listed in Table IV. The distribution of patients in the 4 groups was as follows: 54 had normal LV mass and volume, 67 had concentric LV hypertrophy, 71 had eccentric LV hypertrophy, and 10 patients had isolated LV volume overload. The mean ± standard deviation and range of the LV dimensions of the 4 groups categorized on indexed LV volume and mass are listed in Table V for both measurement conventions.

Relative wall thickness studied in these 4 groups (Table VI) revealed that only 46 of the 67 patients (68%) with concentric LV hypertrophy had relative wall thickness ≥45%, whereas 61 (85.9%) of the 71 patients with eccentric LV hypertrophy were found to have a relative wall thickness <45%. Moreover, not all the patients with normal LV mass and volume (group 1) had relative wall thickness <45%. Indeed, this value was found in only 26 of the 55 patients (47.3%) with normal LV mass and volume. The 10 patients with isolated LV volume overload all had relative wall thickness <45% (mean 22.087 ± 4.873).

DISCUSSION

Grossman et al[14] in a clinical angiographic study concluded that the ratio of the wall thickness h to the LV radius R (h/R) was almost similar in patients with normal LV geometry (0.34 ± 0.02) and those with volume overload (0.38 ± 0.02) compared with higher values (0.58 ± 0.05) in patients with chronic pressure overload. However, the number of patients in each group in their study[14] was small (normal subjects 6; pressure overload, 6; volume overload, 18); the number of patients with volume overload included 3 with a normal LV mass index of 86, 107 and 114 g/m^2, respectively.

In the work of Grossman et al,[14] h/R was not able to distinguish the 3 patients with volume overload, normal LV mass and low h/R ratio from the other patients

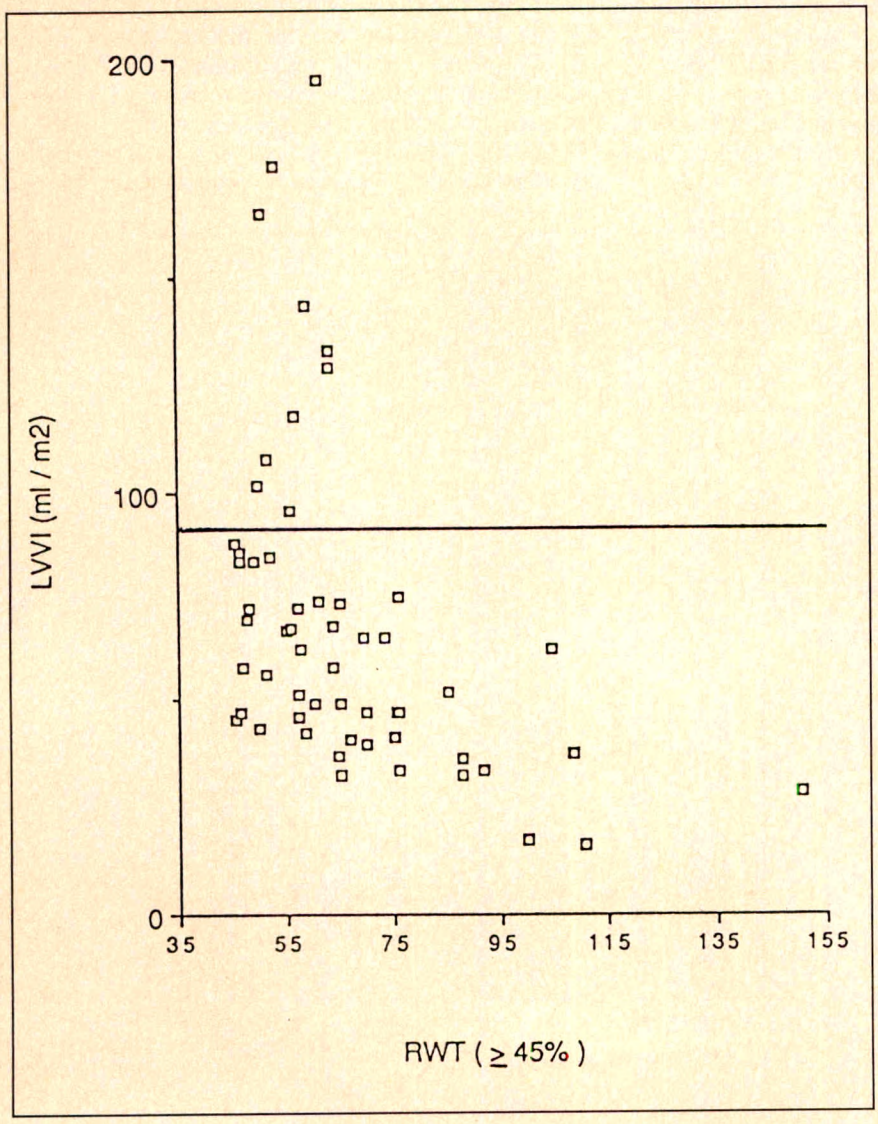


FIGURE 3. Relative wall thickness (RWT) versus indexed left ventricular volume (LVVI) (ml/m^2) in patients with concentric left ventricular hypertrophy according to the Framingham classification.

with volume overload with increased LV mass. Moreover, the actual volumes of the left ventricle were not mentioned in their study.

In the present study, 10 patients are described who have a normal LV mass with enlarged LV volume, a mean relative wall thickness of 22.087 ± 4.873, and who have a quite distinctive LV geometry (isolated LV volume overload) compared with the other 3 groups. This indicates that the only possible way to diagnose isolated LV volume overload from M-mode echo is by actual measurement of the indexed masses and volumes.

Although this proposed echocardiographic category of LV geometry has not been described previously, Casale et al[15] described 3 hearts at postmortem that exhibited the geometric appearances of the isolated volume overload described in this paper. These hearts were dilated but their weights were within normal limits. It is suggested that these findings support our own results defining the presence of this geometric entity, which is admittedly uncommon.

There were other limitations in using the relative wall thickness for the classification of LV hypertrophy. In the Framingham Study,[7] when concentric LV hypertrophy was diagnosed on the basis of relative wall thickness ≥45%, 3 of 170 women (2%) and 3 of 113 men (3%) had slightly dilated left ventricles. In the present study, 10 of the 54 patients (18%) diagnosed as having concentric LV hypertrophy on the basis of relative wall thickness ≥45% had indexed LV volumes exceeding 90 ml/m^2, whereas 20 of 82 patients (24%) with eccentric LV hypertrophy had indexed LV volumes <90 ml/m^2. Moreover, in the Framingham Study, nondilated eccen-

TABLE III Proposed New M-Mode Classification System

Classification	Indexed LV Mass	Indexed LV Volume
Normal LV mass and volume	Normal*	Normal†
Concentric LV hypertrophy	Increased	Normal†
Eccentric LV hypertrophy	Increased	Increased
Isolated LV volume overload	Normal*	Increased

*Penn convention <132 g/m^2 (men); <109 g/m^2 (women).
†American Society of Echocardiographers convention = <90 ml/m^2 (men/women).
LV = left ventricular.

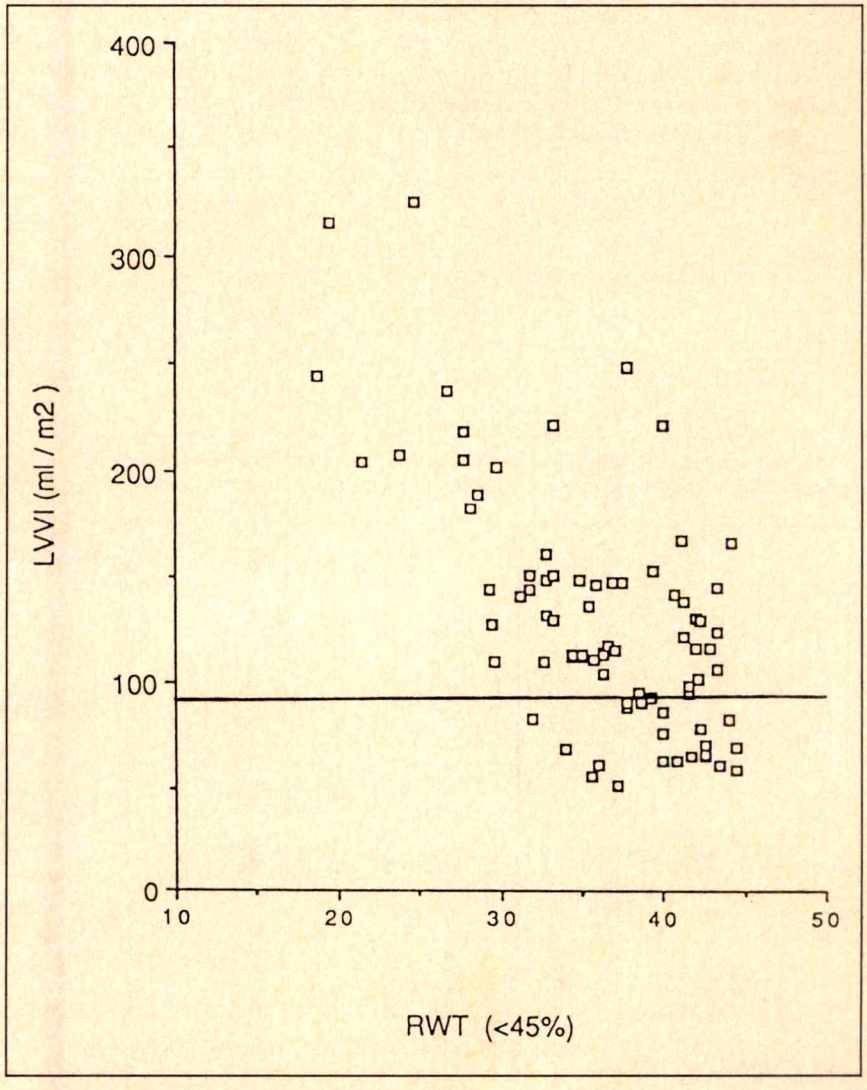


FIGURE 4. Relative wall thickness (RWT) versus indexed left ventricular volume (LVVI) (ml/m^2) in patients with eccentric left ventricular hypertrophy according to the Framingham classification.

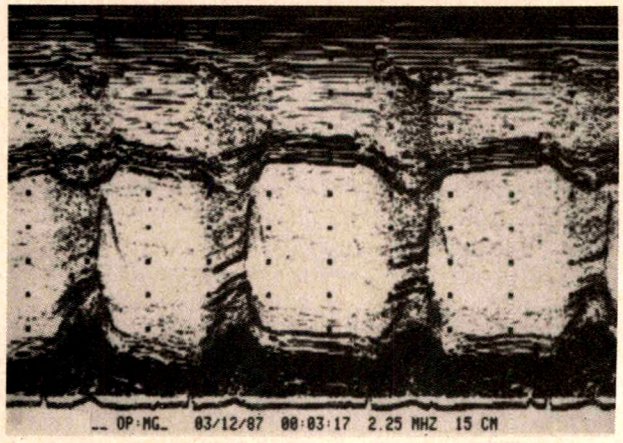


FIGURE 5. M-mode echocardiogram of a patient with isolated LV volume overload diagnosed by the new classification based on mass/volume. The echo shows a dilated left ventricle at the expense of thin LV walls, hence a normal mass. This patient had dilated cardiomyopathy.

TABLE IV Mean ± SD and Range of Indexed Left Ventricular Mass and Left Ventricular Volume (American Society of Echocardiographers and Penn) of the Four Categories in the Proposed New Classification System (men and women combined)

Group		LV Mass (Penn) (g/m^2)	LV Volume (ASE) (ml/m^2)
1—Normal LV mass and volume	Mean ± SD	99 ± 17	56 ± 18
(n = 54)	Range	65 → 130	17 → 89
2—Concentric LV hypertrophy	Mean ± SD	173 ± 50	58 ± 18
(n = 67)	Range	117 → 350	16 → 89
3—Eccentric LV hypertrophy	Mean ± D	219 ± 81	148 ± 49
(n = 71)	Range	116 → 505	92 → 325
4—Isolated LV volume overload	Mean ± SD	96 ± 18	144 ± 37
(n = 10)	Range	71 → 129	92 → 213

Abbreviations as in Table II.

tric LV hypertrophy (increased LV mass but with relative wall thickness <45% and normal indexed LV internal dimension at end-diastole) constituted the most frequent type of LV hypertrophy.[7] However, pathophysiologically eccentric LV hypertrophy occurs in response to volume overload (i.e., a dilated left ventricle) and the h/R ratio remains almost normal.[3,14]

Our findings with respect to the use of relative wall thickness and, on close inspection, the results from the Framingham Study, demonstrate limitations in this diagnostic echocardiographic criterion, especially when a cutoff point of 45% is used in classifying LV hypertrophy into dilated and nondilated types. The main limita-

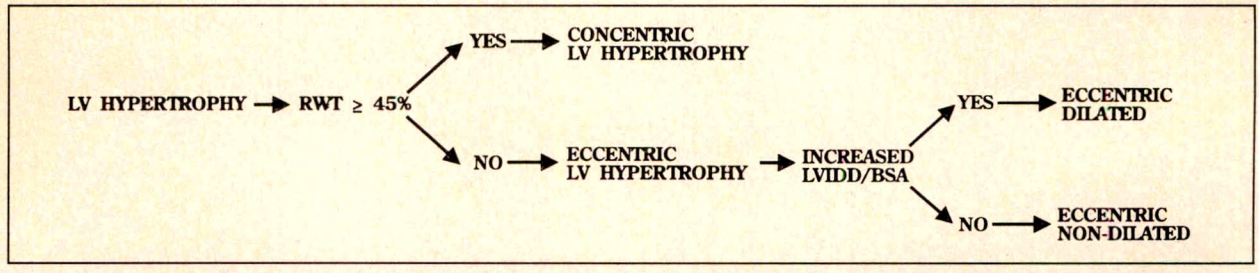


FIGURE 6. Schematic illustration of the Framingham classification of left ventricular (LV) hypertrophy on M-mode echocardiograms. BSA = body surface area; LVIDD = left ventricular internal dimension at end-diastole; RWT = relative wall thickness.

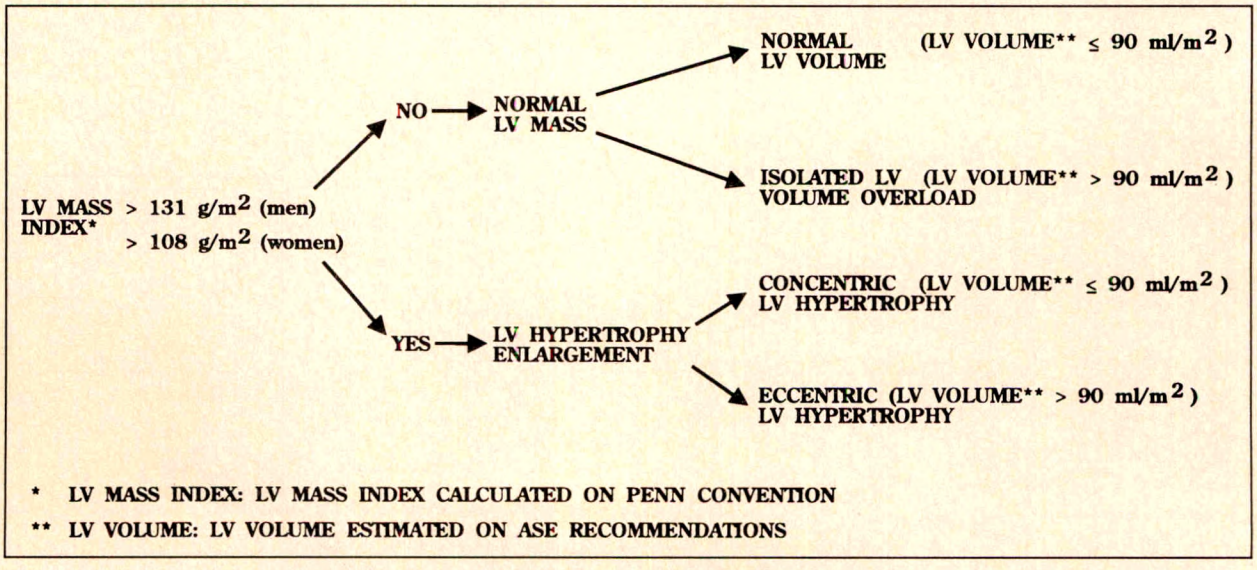


FIGURE 7. Schematic illustration of the proposed classification of left ventricular (LV) geometry.

TABLE V Mean ± SD and Range of Left Ventricular Dimensions by Both ASE and Penn Conventions of the Four Echo Groups* Obtained on the Basis of Mass/Volume Relation

	Interventricular Septum (cm)		LV Posterior Wall (cm)		LV Internal Diastolic Dimension (cm)	
Group	Mean ± SD	Range	Mean ± SD	Range	Mean ± SD	Range
1—ASE	1.1 ± 0.2	(0.7–1.7)	1.1 ± 0.2	(0.7–1.8)	4.5 ± 0.5	(3.0–5.5)
PENN	0.9 ± 0.2	(0.5–1.4)	1.0 ± 0.2	(0.6–1.7)	4.6 ± 0.5	(3.1–5.6)
2—ASE	1.6 ± 0.4	(0.9–2.6)	1.3 ± 0.4	(0.8–2.7)	4.5 ± 0.5	(2.9–5.5)
PENN	1.4 ± 0.4	(0.7–2.2)	1.2 ± 0.4	(0.7–2.6)	4.8 ± 0.5	(3.3–5.7)
3—ASE	1.3 ± 0.4	(0.5–2.7)	1.2 ± 0.3	(0.7–2.0)	6.2 ± 0.7	(5.0–8.2)
PENN	1.1 ± 0.4	(0.5–2.5)	1.1 ± 0.2	(0.6–1.8)	6.4 ± 0.7	(5.2–8.4)
4—ASE	0.8 ± 0.1	(0.5–1.0)	0.7 ± 0.1	(0.5–1.0)	6.2 ± 0.6	(5.3–7.0)
PENN	0.6 ± 0.2	(0.4–1.0)	0.6 ± 0.1	(0.4–0.8)	6.4 ± 0.6	(5.5–7.2)

*Defined in Table IV.
Abbreviations as in Table II.

tion of relative wall thickness has been stressed by Gaasch,[16] namely, that minor measurement errors potentially limit its extensive use in clinical cardiology. However, relative wall thickness is liable to error in the measurement of LV dimensions so that when the posterior wall of the left ventricle is under or overestimated, this will be reflected on the internal dimension and thus, seriously affect the h/R ratio. Moreover, an applicable cutoff point of relative wall thickness, which is useful in well-defined groups of patients such as those of Grossman et al[14] or a sample of the general population,[7] may not readily transfer into a sample of cardiac patients whose LV hypertrophy may be associated with (1) deranged coronary flow due to valvular disease which in turn, may affect the myocardial growth; (2) valvular disease progressing to cardiac hypertrophy; and (3) acute cardiac failure in which the h/R ratio is very sensitive because acute dilatation causes simultaneous increase of the radius and decrease in wall thickness.[3] Furthermore, in the present study, there were some patients who had mixed volume and pressure overload, others with coronary artery disease, and patients with LV hypertrophy due to dilatation of the left ventricle after myocardial infarction. In the present study, the mixture of various cardiovascular pathologic conditions encountered in routine cardiologic practice highlights the anomalies in classifying LV enlargement on the basis of relative wall thickness.

Estimation of the indexed LV volumes from M-mode echocardiograms may also be affected by error in the echo measurements, especially because the volume of the left ventricle is derived from the cube of its internal diameter. However, the classification of LV geometry on the basis of mass/volume relationship allows echocardiographic detection of patients with isolated LV volume overload. This may have important prognostic implications, especially when both LV hypertrophy[17] and LV dilatation[18,19] have been shown to be important predictors of survival in various cardiovascular disorders.

There is indirect evidence to support this in patients with dilated cardiomyopathy with depressed LV function. Feild et al[20] found that both ejection fraction and mass/volume ratio were of prognostic value and were useful indexes for classification of patients with dilated cardiomyopathy and depressed ejection fraction. The mass/volume ratio was used as representative of the relative degree of hypertrophy and patients with a mass/volume ratio <0.90 had poorer prognosis than those with a ratio in excess of this value.

TABLE VI Relative Wall Thickness in the Four Groups of Patients in This Study Classified on the Basis of Indexed Left Ventricular Volume and Mass

		Relative Wall Thickness		
Group	Total No.	Criterion (%)	Positive	%
Normal LV mass and volume	55	≥45	29	53
Concentric LV hypertrophy	66	≥45	46	70
Eccentric LV hypertrophy	71	<45	61	86
Isolated LV volume overload	10	<45	10	100

LV = left ventricular.

Finally, it could be argued that M-mode measurements may not be accurate for calculating LV volume in the presence of myocardial infarction.[21] The patients included in this study represented a sample of the cardiac population and included 11 with myocardial infarction. Notwithstanding this, all the M-mode echocardiograms in the study were directed by 2-dimensional echocardiograms and none of these patients had LV aneurysm. The basic aim of the study was to relate LV volume and mass in order to classify LV hypertrophy/enlargement. Woythaler et al[22] demonstrated that M-mode estimates of LV mass correlated better with the weight of the left ventricle at autopsy than estimates of 2-dimensional echocardiography. Therefore, it was believed that both LV volumes and masses should be estimated from M-mode measurements in order to keep consistency in the method.

Acknowledgment: We wish to thank Francis G. Dunn, FRCP, for his critical review of the manuscript.

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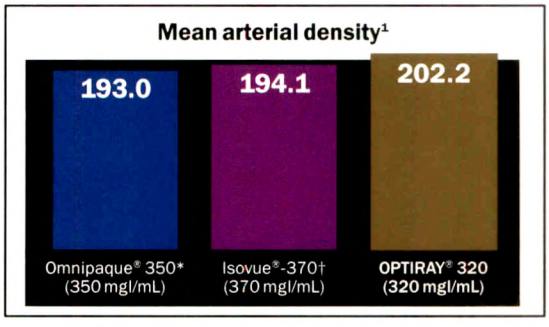


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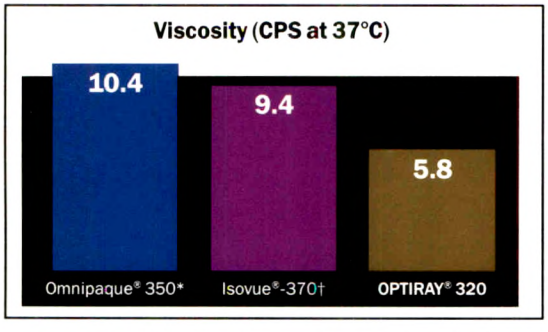
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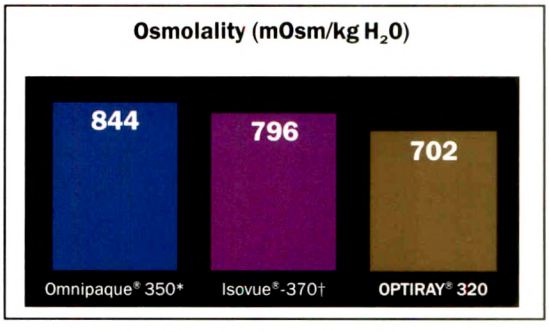


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DESCRIPTION: Each milliliter of OPTIRAY 160 (ioversol injection 34%) provides 339 mg of ioversol with 3.6 mg of tromethamine as a buffer and 0.2 mg of edetate calcium disodium as a stabilizer. OPTIRAY 160 provides 16% (160 mg/mL) organically bound iodine.

Each milliliter of OPTIRAY 240 (ioversol injection 51%) provides 509 mg of ioversol with 3.6 mg of tromethamine as a buffer and 0.2 mg of edetate calcium disodium as a stabilizer. OPTIRAY 240 provides 24% (240 mg/mL) organically bound iodine.

Each milliliter of OPTIRAY 320 (ioversol injection 68%) provides 678 mg of ioversol with 3.6 mg of tromethamine as a buffer and 0.2 mg of edetate calcium disodium as a stabilizer. OPTIRAY 320 provides 32% (320 mg/mL) organically bound iodine.

Each milliliter of OPTIRAY 350 (ioversol injection 74%) provides 741 mg of ioversol with 3.6 mg of tromethamine as a buffer and 0.2 mg of edetate calcium disodium as a stabilizer. OPTIRAY 350 provides 35% (350 mg/mL) organically bound iodine.

CONTRAINDICATIONS: None.

WARNINGS: Nonionic iodinated contrast media inhibit blood coagulation, in vitro, less than ionic contrast media. Clotting has been reported when blood remains in contact with syringes containing nonionic contrast media.

Serious, rarely fatal, thromboembolic events causing myocardial infarction and stroke have been reported during angiographic procedures with both ionic and nonionic contrast media. Therefore, meticulous intravascular administration technique is necessary, particularly during angiographic procedures, to minimize thromboembolic events. Numerous factors, including length of procedure, catheter and syringe material, underlying disease state and concomitant medications may contribute to the development of thromboembolic events. For these reasons, meticulous angiographic techniques are recommended including close attention to guidewire and catheter manipulation, use of manifold systems and/or three-way stopcocks, frequent catheter flushing with heparinized saline solutions and minimizing the length of the procedure. The use of plastic syringes in place of glass syringes has been reported to decrease but not eliminate the likelihood of in vitro clotting.

Serious or fatal reactions have been associated with the administration of iodine-containing radiopaque media. It is of utmost importance to be completely prepared to treat any contrast medium reaction.

As with any contrast medium, serious neurologic sequelae, including permanent paralysis, can occur following cerebral arteriography, selective spinal arteriography and arteriography of vessels supplying the spinal cord. A cause-effect relationship to the contrast medium has not been established since the patients' pre-existing condition and procedural technique are causative factors in themselves. The arterial injection of a contrast medium should never be made following the administration of vasopressors since they strongly potentiate neurologic effects.

Caution must be exercised in patients with severely impaired renal function, combined renal and hepatic disease, severe thyrotoxicosis, myelomatosis, or anuria, particularly when large doses are administered.

Intravascularly administered iodine-containing radiopaque media are potentially hazardous in patients with multiple myeloma or other paraproteinemia, particularly in those with therapeutically resistant anuria. Myeloma occurs most commonly in persons over age 40. Although neither the contrast agent nor dehydration has been proved separately to be the cause of anuria in myelomatous patients, it has been speculated that the combination of both may be causative. The risk in myelomatous patients is not a contraindication to the procedure; however, special precautions, including maintenance of normal hydration and close monitoring, are required. Partial dehydration in the preparation of these patients prior to injection is not recommended since this may predispose the patient to precipitation of the myeloma protein.

Administration of radiopaque materials to patients known or suspected of having pheochromocytoma should be performed with extreme caution. If, in the opinion of the physician, the possible benefits of such procedures outweigh the considered risks, the procedures may be performed; however, the amount of radiopaque medium injected should be kept to an absolute minimum. The blood pressure should be assessed throughout the procedure, and measures for treatment of a hypertensive crisis should be available.

Contrast media may promote sickling in individuals who are homozygous for sickle cell disease when administered intravascularly.

Reports of thyroid storm following the intravascular use of iodinated radiopaque agents in patients with hyperthyroidism or with an autonomously functioning thyroid nodule, suggest that this additional risk be evaluated in such patients before use of any contrast medium.

PRECAUTIONS: *General:* Diagnostic procedures which involve the use of iodinated intravascular contrast agents should be carried out under the direction of personnel skilled and experienced in the particular procedure to be performed. A fully equipped emergency cart, or equivalent supplies and equipment, and personnel competent in recognizing and treating adverse reactions of all types should always be available. Since severe delayed reactions have been known to occur, emergency facilities and competent personnel should be available for at least 30 to 60 minutes after administration.

Preparatory dehydration is dangerous and may contribute to acute renal failure in patients with advanced vascular disease, diabetic patients, and in susceptible non-diabetic patients (often elderly with pre-existing renal disease). *Patients should be well hydrated prior to and following the administration of OPTIRAY.*

The possibility of a reaction, including serious, life-threatening, fatal, anaphylactoid or cardiovascular reactions, should always be considered (See ADVERSE REACTIONS). Increased risk is associated with a history of previous reaction to a contrast medium, a known sensitivity to iodine and known allergies (i.e., bronchial asthma, hay fever and food allergies) or hypersensitivities.

The occurrence of severe idiosyncratic reactions has prompted the use of several pretesting methods. However, pretesting cannot be relied upon to predict severe reactions and may itself be hazardous to the patient. It is suggested that a thorough medical history with emphasis on allergy and hypersensitivity, prior to the injection of any contrast medium, may be more accurate than pretesting in predicting potential adverse reactions. A positive history of allergies or hypersensitivity does not arbitrarily contraindicate the use of a contrast agent when a diagnostic procedure is thought essential, but caution should be exercised. Premedication with antihistamines or corticosteroids to avoid or minimize possible allergic reactions in such patients should be considered. Reports indicate that such pretreatment does not prevent serious life-threatening reactions, but may reduce both their incidence and severity.

General anesthesia may be indicated in the performance of some procedures in selected patients; however, a higher incidence of adverse reactions has been reported in these patients, and may be attributable to the inability of the patient to identify untoward symptoms or to the hypotensive effect of anesthesia which can prolong the circulation time and increase the duration of exposure to the contrast agent.

In angiographic procedures, the possibility of dislodging plaques or damaging or perforating the vessel wall should be considered during catheter manipulations and contrast medium injection. Test injections to insure proper catheter placement are suggested.

Angiography should be avoided whenever possible in patients with homocystinuria because of the risk of inducing thrombosis and embolism.

Patients with congestive heart failure should be observed for several hours following the procedure to detect delayed hemodynamic disturbances which may be associated with a transitory increase in the circulating osmotic load.

Selective coronary arteriography should be performed only in selected patients and those in whom the expected benefits outweigh the procedural risk. The inherent risks of angiocardiography in patients with chronic pulmonary emphysema must be weighed against the necessity for performing this procedure.

Extreme caution during injection of a contrast medium is necessary to avoid extravasation. This is especially important in patients with severe arterial or venous disease.

Drug Interactions: Renal toxicity has been reported in a few patients with liver dysfunction who were given oral cholecystographic agents followed by intravascular contrast agents. Administration of any intravascular contrast agent should therefore be postponed in patients who have recently received a cholecystographic contrast agent.

Other drugs should not be mixed with ioversol injection.

Drug Laboratory Test Interactions: The results of PBI and radioactive iodine uptake studies, which depend on iodine estimation, will not accurately reflect thyroid function for up to 16 days following administration of iodinated contrast media. However, thyroid function tests not depending on iodine estimations, e.g., T3 resin uptake and total or free thyroxine (T4) assays are not affected.

Carcinogenesis, Mutagenesis, Impairment of Fertility: No long term animal studies have been performed to evaluate carcinogenic potential. However, animal studies suggest that this drug is not mutagenic and does not affect fertility.

Pregnancy Category B: No teratogenic effects attributable to ioversol have been observed in teratology studies performed in animals. There are, however, no adequate and well controlled studies in pregnant women. It is not known whether ioversol crosses the placental barrier or reaches fetal tissues. However, many injectable contrast agents cross the placental barrier in humans and appear to enter fetal tissue passively. Because animal teratology studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed. X-ray procedures involve a certain risk related to the exposure of the fetus.

Nursing Mothers: It is not known whether ioversol is excreted in human milk. However, many injectable contrast agents are excreted unchanged in human milk. Although it has not been established that serious adverse reactions occur in nursing infants, caution should be exercised when intravascular contrast media are administered to nursing women because of potential adverse reactions, and consideration should be given to temporarily discontinuing nursing.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: Adverse reactions following the use of OPTIRAY formulations are usually mild to moderate, of short duration and resolve spontaneously (without treatment). However, serious, life-threatening and fatal reactions, mostly of cardiovascular origin, have been associated with the administration of iodine-containing contrast media.

Injections of contrast media are often associated with sensations of warmth and pain. In controlled double-blind clinical studies, significantly less warmth and pain were associated with the injection of OPTIRAY than with iothalamate meglumine, diatrizoate meglumine, and diatrizoate meglumine and diatrizoate sodium.

When OPTIRAY was used for coronary arteriography and ventriculography in double-blind clinical trials, electrocardiographic and hemodynamic changes occurred with less frequency and severity with ioversol injection than with diatrizoate meglumine and diatrizoate sodium.

Following coronary artery and left ventricular injection, electrocardiographic parameters were affected less with OPTIRAY (ioversol injection) than with diatrizoate meglumine and diatrizoate sodium injection. These parameters included the following: bradycardia, tachycardia, T-wave amplitude, ST depression and ST elevation.

OPTIRAY has also been shown to cause fewer changes in cardiac function and systemic blood pressure than conventional ionic media. These include cardiac output, left ventricular systolic and end-diastolic pressure, right ventricular systolic and pulmonary artery systolic pressures and decreases in systolic and diastolic blood pressures.

The following table of incidence of reactions is based upon clinical trials with OPTIRAY formulations in over 1466 patients. This listing includes all adverse reactions which were coincidental to the administration of ioversol regardless of their direct attributability to the drug or the procedure. Adverse reactions are listed by organ system and in decreasing order of occurrence. Significantly more severe reactions are listed before others in a system regardless of frequency.

Adverse Reactions

System	> 1%	≤ 1%
Cardiovascular	none	angina pectoris hypotension blood pressure fluctuation arterial spasm bradycardia conduction defect false aneurysm hypertension transient arrhythmia vascular trauma
Digestive	none	nausea vomiting
Nervous	none	cerebral infarct headache blurred vision vertigo lightheadedness vasovagal reaction disorientation paresthesia dysphasia muscle spasm syncope visual hallucination
Respiratory	none	laryngeal edema pulmonary edema sneezing nasal congestion coughing shortness of breath hypoxia
Skin	none	periorbital edema urticaria facial edema flush pruritus
Miscellaneous	none	extravasation hematoma shaking chills bad taste general pain

Regardless of the contrast medium employed, the overall incidence of serious adverse reaction is higher with coronary arteriography than with other procedures. Cardiac decompensation, serious arrhythmias, myocardial ischemia or myocardial infarction may occur during coronary arteriography and left ventriculography.

General Adverse Reactions to Contrast Media

The following adverse reactions are possible with any parenterally administered iodinated contrast medium. Severe life-threatening reactions and fatalities, mostly of cardiovascular origin, have occurred. Most deaths occur during injection or 5 to 10 minutes later; the main feature being cardiac arrest with cardiovascular disease as the main aggravating factor. Isolated reports of hypotensive collapse and shock are found in the literature. Based upon clinical literature, reported deaths from the administration of conventional iodinated contrast agents range from 6.6 per 1 million (0.00066 percent) to 1 in 10,000 patients (0.01 percent).

The reported incidence of adverse reactions to contrast media in patients with a history of allergy is twice that of the general population. Patients with a history of previous reactions to a contrast medium are three times more susceptible than other patients. However, sensitivity to contrast media does not appear to increase with repeated examinations.

Adverse reactions to injectable contrast media fall into two categories: chemotoxic reactions and idiosyncratic reactions.

Chemotoxic reactions result from the physicochemical properties of the contrast medium, the dose and the speed of injection. All hemodynamic disturbances and injuries to organs or vessels perfused by the contrast medium are included in this category.

Idiosyncratic reactions include all other reactions. They occur more frequently in patients 20 to 40 years old. Idiosyncratic reactions may or may not be dependent on the dose injected, the speed of injection, the mode of injection and the radiographic procedure. Idiosyncratic reactions are subdivided into minor, intermediate and severe. The minor reactions are self-limited and of short duration; the severe reactions are life-threatening and treatment is urgent and mandatory.

In addition to the adverse reactions reported for ioversol, the following additional adverse reactions have been reported with the use of other contrast agents and are possible with any water soluble, iodinated contrast agent.

Nervous: convulsions, aphasia, paralysis, visual field losses which are usually transient but may be permanent, coma and death.

Cardiovascular: angioneurotic edema, peripheral edema, vasodilation, thrombosis and rarely thrombophlebitis, disseminated intravascular coagulation and shock.

Skin: maculopapular rash, erythema, conjunctival symptoms, ecchymosis and tissue necrosis.

Respiratory: choking, dyspnea, wheezing which may be an initial manifestation of more severe and infrequent reactions including asthmatic attack, laryngospasm and bronchospasm, apnea and cyanosis. Rarely these allergic-type reactions can progress into anaphylaxis with loss of consciousness, coma, severe cardiovascular disturbances and death.

Miscellaneous: hyperthermia, temporary anuria or other nephropathy.

Other reactions may also occur with the use of any contrast agent as a consequence of the procedural hazard; these include hemorrhage or pseudoaneurysms at the puncture site, brachial plexus palsy following axillary artery injections, chest pain, myocardial infarction, and transient changes in hepatorenal chemistry tests. Arterial thrombosis, displacement of arterial plaques, venous thrombosis, dissection of the coronary vessels and transient sinus arrest are rare complications.

In cerebral arteriography, cardiovascular reactions that may occur with some frequency are bradycardia and either an increase or decrease in systemic blood pressure. Neurological reactions that may occur are: seizures, drowsiness, transient paresis, and mild disturbances in vision.

Central nervous system reactions with OPTIRAY in controlled clinical studies in cerebral arteriography that were considered drug-related and occurred with frequencies greater than 1% were: headache, bradycardia, blood pressure fluctuation, disorientation, nausea and vertigo.

In aortography, depending on the technique employed, the risks of this procedure also include the following: injury to the aorta and neighboring organs, pleural puncture, renal damage including infarction and acute tubular necrosis with oliguria and anuria, retroperitoneal hemorrhage from the translumbar approach and spinal cord injury and pathology associated with the syndrome of transverse myelitis. Under conditions of slowed aortic circulation there is an increased likelihood for aortography to cause muscle spasm. Occasional serious neurologic complications, including paraplegia, have also been reported in patients with aortoiliac obstruction, femoral artery obstruction, abdominal compression, hypotension, hypertension, spinal anesthesia, and injection of vasopressors to increase contrast. In these patients the concentration, volume, and number of repeat injections of the medium should be maintained at a minimum with appropriate intervals between injections. The position of the patient and catheter tip should be carefully monitored.

Entry of a large aortic dose into the renal artery may cause, even in the absence of symptoms, albuminuria, hematuria, and an elevated creatinine and urea nitrogen. Rapid and complete return of function usually follows.

There were no cardiovascular system reactions with OPTIRAY in controlled clinical studies in coronary arteriography with left ventriculography that were considered drug-related and occurred with a frequency greater than 1%.

PRECAUTIONS FOR SPECIFIC PROCEDURES:

Cerebral Arteriography

Extreme caution is advised in patients with advanced arteriosclerosis, severe hypertension, cardiac decompensation, senility, recent cerebral thrombosis or embolism, and migraine.

Peripheral Arteriography

Pulsation should be present in the artery to be injected. In thromboangiitis obliterans, or ascending infection associated with severe ischemia, angiography should be performed with extreme caution, if at all.

Coronary Arteriography and Left Ventriculography

Mandatory prerequisites to the procedure are specialized personnel, ECG monitoring apparatus and adequate facilities for immediate resuscitation and cardioversion. Electrocardiograms and vital signs should be routinely monitored throughout the procedure.

Venography

Special care is required when venography is performed in patients with suspected thrombosis, phlebitis, severe ischemic disease, local infection or a totally obstructed venous system. In order to minimize extravasation during injection, fluoroscopy is recommended.

Intravenous Digital Subtraction Angiography

In addition to the general precautions previously described, the risks associated with IV DSA include those usually attendant with catheter procedures and include intramural injections, vessel dissection and tissue extravasation. The potential risk is reduced when small test injections of contrast medium are made under fluoroscopic observation to insure that the catheter tip is properly positioned and, in the case of peripheral placement, that the vein is of adequate size.

Patient motion, including respiration and swallowing, can result in misregistration leading to image degradation and non-diagnostic studies.

OVERDOSAGE: The adverse effects of overdosage are life-threatening and affect mainly the pulmonary and cardiovascular system. Treatment of an overdosage is directed toward the support of all vital functions, and prompt institution of symptomatic therapy.

Ioversol does not bind to plasma or serum protein and is therefore, dialyzable.

The intravenous LD_{50} values (gl/kg) for ioversol in animals were: 17 (mice), and 15 (rats).

DOSAGE AND ADMINISTRATION: Details on dosage are provided in the package insert. CONSULT FULL PACKAGE INSERT BEFORE USE.

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Association Between Residual Mitral Regurgitation and Left Ventricular Outflow Obstruction After Carpentier Ring Mitral Annuloplasty

Paul A. Tunick, MD, David G. Cziner, MD, Edward S. Katz, MD, John L. Perez, MA, and Itzhak Kronzon, MD

In 1971, Carpentier et al[1] reported the use of a new technique for mitral valve repair using an annuloplasty ring. Although this technique avoids some complications of prosthetic valves, spatial changes in the mitral apparatus after this operation may result in systolic anterior motion of the mitral valve which may cause left ventricular (LV) outflow obstruction similar to that seen in hypertrophic cardiomyopathy.[2,3] In a series of 439 patients, systolic anterior motion was seen in 6.4% of patients after Carpentier ring repair, and LV outflow obstruction was present in 2.3%.[4] Although outflow obstruction may be treated successfully medically,[4] it may also be a cause of immediate (intraoperative) failure of the technique.[5] We have previously reported a relation between mitral regurgitation (MR) and LV outflow obstruction in 2 groups. In those who have undergone aortic valve replacement for aortic stenosis, the relief of outflow obstruction after aortic valve replacement was associated with a significant reduction in the degree of MR.[6] In the second group, those with hypertrophic cardiomyopathy, the degree of MR was directly associated with the severity of outflow obstruction.[7] The current study evaluates the possible mechanisms of LV outflow obstruction after Carpentier ring mitral annuloplasty, and investigates the relation, if any, of MR to the presence of LV outflow obstruction.

Between June 1987 and July 1991, Doppler echocardiography was performed on 352 patients following Carpentier ring mitral annuloplasty. Mitral systolic anterior motion was present in 43 patients (12%) with ages ranging from 21 to 83 (mean 60) years, including 30 men (70%). The studies were done from 2 days to 7 years after surgery. These echocardiograms were reviewed.

M-mode, 2-dimensional, pulsed, continuous-wave, and color flow Doppler studies were performed on a Hewlett-Packard Sonos 500 system (Andover, Massachusetts). The presence of LV outflow obstruction was documented by pulsed Doppler in the outflow tract, and the gradient was measured from the apical view using continuous-wave Doppler and the modified Bernoulli equation. A velocity of ≥2 m/s was considered abnormal. The degree of MR was graded using previously described methods.[8] Because normal people may have no or mild MR,[9] the group with no or mild MR was compared with the group with significant, abnormal degrees of MR (moderate or severe). Since the grading of MR and the measurement of the outflow velocity were done before this retrospective review, they were evaluated blindly. At study, the following additional measurements were also obtained: LV diastolic dimension, LV systolic dimension, LV ejection fraction, left atrial size, LV outflow size, and Carpentier ring diameter. The outflow size was measured from the anterior part of the Carpentier ring to the ventricular septum. The ring diameter was measured as the distance between the centers of the 2 bright circular echoes consisting of the anterior and posterior edges of the ring. The latter 2 dimensions (outflow and ring size) were measured from the parasternal long-axis view.

Values are presented with means and standard errors of the mean. A Pearson product-moment correlation coefficient was calculated to assess the relation between variables. Linear regression was done with outflow gradient as the dependent variable. The prevalence of significant (moderate or severe) MR was compared in patients with and without mitral systolic anterior motion by the chi-square test. A p value <0.05 was considered significant.

Mitral systolic anterior motion was seen in 43 patients after Carpentier ring repair (12%). The distribution of LV outflow gradients in these 43 patients is listed in Table I. There was no gradient in 23 patients (54%), and the gradients in the other 20 patients ranged from 16 to 140 mm Hg. The mean gradient in the study group was 24 ± 5.1.

There was a significantly higher incidence of moderate or severe MR in the group of 43 patients with (33%) than in the 309 patients without (19%) systolic anterior motion ($p = 0.05$) (Table II). In those with systolic anterior motion, MR was absent or mild in 29 patients (67%), moderate in 10 patients (23%) and severe in 4 patients (9%). In the 309 patients without systolic anterior motion, MR was moderate in 41 (13%) and severe in 19 (6%).

In the group with systolic anterior motion, mean LV outflow gradient in those with absent or mild MR was 15 ± 5 mm Hg. Mean gradient in those with moderate MR

TABLE I Distribution of Outflow Tract Gradients

Gradient (mm Hg)	Frequency (no. of pts.)	%
0	23	53.5
16	3	7
20	1	2.3
25	2	4.7
36	2	4.7
40	1	2.3
50	2	4.7
64	5	11.7
70	2	4.7
100	1	2.3
140	1	2.3

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TABLE II Mitral Regurgitation in Patients With and Without Systolic Anterior Motion

	0-1+ MR	2-3+ MR
SAM	29 (67%)	14 (33%)
No SAM	249 (81%)	60 (19%)

p = 0.05.
MR = mitral regurgitation; SAM = systolic anterior motion.

TABLE III Distribution of Gradients with Respect to Mitral Regurgitation

Outflow Gradient (mm Hg)	0–Mild MR	Moderate MR	Severe MR
140			·
120			
100			·
80			
	· ·		
	·	· · ·	·
60			
	·		·
40	·		
	·	·	
20	· · ·		
	· · ·		
0	***(n = 17)	· · · · · ·	

MR = mitral regurgitation.
Each dot represents an individual patient.
The 3 asterisks represent 17 patients.

TABLE IV Variables Not Correlated with Gradient

Variable	Range	Mean
Left ventricle (diastole) (mm)	39–66	50 ± 1
Left ventricle (systole) (mm)	20–48	36 ± 1
Ejection fraction (%)	36–87	59 ± 2
Left atrium (mm)	34–99	54 ± 2
Left ventricular outflow tract (mm)	11–25	18 ± 1
Carpentier ring diameter (mm)	16–26	21 ± 0.3

was 23 ± 10 mm Hg, and in those with severe MR 89 ± 20 mm Hg (Table III).

The distributions of LV diastolic and systolic dimensions, LV ejection fractions, left atrial sizes, outflow tract diameters, and ring diameters in patients with systolic anterior motion are detailed in Table IV. The determination of correlation coefficients showed that the only significant relation among all of these variables was between MR and LV outflow tract gradient ($r = 0.54$, $p = 0.005$). Although the r value is not high, this does explain 29% of the effect. There was no significant correlation between the outflow tract diameter, LV size or ejection fraction, left atrial size or ring diameter, and the outflow tract gradient. Linear regression showed that the outflow gradient was dependent on the degree of MR (β coefficient = 27.4, constant = 14.9, $p = 0.0002$).

Subsequent echocardiograms were available in 16 of 20 patients (80%) with outflow gradients, recorded 1 week to 15 months after the first study. Of these 16 patients, half (8) had MR that was moderate or severe. The outflow gradient decreased over time to zero in 6 of these 8 patients (75%), but there was no predictable effect of this decrease in gradient on the degree of MR (MR decreased in 3 and increased in 3 as the gradient decreased).

The most frequent complication of the Carpentier ring procedure in our 352 patients was significant MR (74 patients, 21%). Of these, 51 patients (14.5%) had moderate and 23 (6.5%) had severe MR. Mitral systolic anterior motion, present in 43 patients (12%), was the next most frequent complication. Other more rare problems were also diagnosed by echocardiography. Abnormal placement of the ring was seen in 2 patients (0.6%). The ring was sewn anterior to the annulus in 1 and attached to the atrial septum in 1. There was partial dehiscence of the ring with paravalvular leaks in 3 patients (0.9%). In addition, the following complications were diagnosed in 1 patient (0.3%) each: torn chordae, a 5 × 7 cm left atrial clot, a vegetation, and a coronary fistula to the left ventricle after myomectomy.

Our previous experience in evaluating the relation between LV outflow obstruction and MR in patients with aortic stenosis[6] and hypertrophic cardiomyopathy[7] led us to hypothesize that a similar relation may exist in patients who develop mitral systolic anterior motion as a complication of the Carpentier ring repair. The current study does confirm that there is such a direct association. It is not possible to say whether MR causes the outflow obstruction or vice versa. In fact, both mechanisms may pertain in different patients. There is a significantly higher incidence of MR in the patients with systolic anterior motion than in those without it.

In addition to MR as a cause of outflow obstruction in patients with systolic anterior motion, we looked further to see if there was a relation between other parameters and the degree of obstruction. Although our laboratory has previously shown that the outflow tract dimension decreases as a result of the Carpentier repair,[10] there was no relation between the postoperative diameter of LV outflow tract and degree of obstruction. In addition, the size of the ring itself had no effect, nor did left atrial or LV dimensions or ejection fraction.

The incidence of mitral systolic anterior motion in our series is relatively high, 12%. Only 44% of these patients had enough systolic anterior motion to result in an LV outflow gradient. This obstruction produced an acute critical problem in only 1 patient. This patient, with the highest gradient (140 mm Hg), had acute deterioration immediately after operation, which responded to medical management. Severe MR eventually disappeared with therapy, which resulted in the disappearance of the outflow gradient. Despite the association between the degree of MR and the degree of obstruction that we have demonstrated, our data show that there is no way to predict the change in the degree of MR as the outflow gradient decreases in an individual patient. This probably indicates that there are multiple mechanisms for the persistence of MR after repair, only some of which are related to the degree of outflow obstruction. Incomplete correction, leaflet degeneration and suture dehiscence have been previously suggested as such mechanisms.[5]

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Aortic Distensibility in Children with the Marfan Syndrome

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The Marfan syndrome is a heritable disease of connective tissue, which predominantly affects the skeletal, ocular and cardiovascular systems.[1] Recent immunohistochemical and genetic findings suggest that the ultimate defect is in fibrillin, a microfibrillar protein abundant in tissues involved in Marfan syndrome.[2] Clinically and in terms of prognosis, dilatation of the aortic root is the key manifestation of the syndrome, because it predisposes the subject to the risk of aortic dissection and fatal rupture, or severe regurgitation and heart failure.[3] Although the structural abnormalities of the Marfan aorta have been well described,[1] its conduit function was poorly known until Hirata et al[4] recently reported on impaired aortic distensibility in adults with the Marfan syndrome. In the present investigation we expanded this approach by studying aortic distensibility with magnetic resonance imaging (MRI)[5] in children and adolescents with this disease.

Children with the Marfan syndrome (11 boys and 13 girls, aged 3.5 to 16 years) were consecutively evaluated and followed-up in 1990 at the Genetics Clinic, Department of Pediatrics, Helsinki University Central Hospital. The diagnosis was based on criteria established at the 7th International Congress of Human Genetics in 1986[6] and at the First International Symposium on Marfan Syndrome in 1988. Diagnostic procedures were the same as in our previous study,[7] and included history, physical examination, complete echocardiographic study and ophthalmologic consultation. Eighteen patients had a positive family history of the Marfan syndrome. All patients were asymptomatic except one 3.5-year-old child who had compensated heart failure due to mitral regurgitation. No patient was receiving β-adrenoceptor blocking drugs.

For a control group, we studied 20 healthy children (9 boys and 11 girls, aged 6.5 to 17 years); they were recruited through their parents who were members of the hospital staff. These children underwent a physical and echocardiographic examination in addition to the study of the thoracic aorta by MRI. Verbal parental consent was obtained for each child participating in the study. The protocol was approved by the local ethics committee.

The studies were performed using a 1.0 Tesla superconducting Siemens unit (Magnetom 42 SP), a body coil and electrocardiogram triggering. To examine changes with the cardiac cycle in the luminal areas of the ascending and descending thoracic aorta, a cine-examination was obtained in a plane transecting the ascending and descending aorta axially at the level of pulmonary artery bifurcation. We used the 2-dimensional gradient echo sequence with a repetition time of 30 ms and an echo time of 12 ms; the flip angle was 60°, the imaging matrix was 128 × 256, and the slice thickness was 7 mm. Another cine-study was obtained in the coronal direction in the plane of the aortic valve.

Diastolic and systolic cross-sectional areas of the ascending and descending thoracic aorta were integrated with a commercially available image analysis system (Radgop/Wiz, Contextvision, Struers Vision AB). The radiologist performing the analyses had no knowledge of the subject under study. Measurements were used to determine the change of the aortic luminal area from end-diastole to end-systole. Aortic distensibility was calculated by the following formula: distensibility = aortic luminal area change/diastolic luminal area × pulse pressure. This measurement is identical to the echocardiographic distensibility measurement,[8] except that aortic luminal areas are substituted for diameters. The pressure-independent aortic stiffness index was calculated by the following formula: stiffness index = ln (systolic/diastolic blood pressure)/(aortic diameter change/aortic diastolic diameter)[9]; diameters were derived from the luminal areas assuming circular geometry. In 4 patients with the Marfan syndrome, MRI measurements suggested a minute reduction of the luminal area of the descending aorta from end-diastole to end-systole, rather than an increase. In calculating aortic distensibility and stiffness index, these measurements

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TABLE I Age and Body Size in Children with the Marfan Syndrome and in Healthy Control Subjects

	Patients (n = 24)	Control Subjects (n = 20)	p Value*
Age (year)	10.5 ± 0.8	11.9 ± 0.7	0.19
Height (cm)	156 ± 6	151 ± 4	0.52
Weight (kg)	46.9 ± 4.8	39.4 ± 2.7	0.20
Body area (m^2)	1.41 ± 0.10	1.28 ± 0.06	0.30

*Student's *t* test.
Data are mean ± SE.

were taken to represent zero change, because there cannot be any true contraction of the aortic lumen during systole. Brachial artery blood pressure was measured immediately before and after the MRI study using a calibrated sphygmomanometer and the cuff method. The average of the 2 pressure readings was used in the calculations. Coronal cine-MRI was used to identify aortic regurgitation and to assess its severity.[10]

To quantify the random error in measuring the aortic luminal areas, 1 radiologist analyzed blindly the studies of 6 subjects twice at an interval of several days. The square root of the mean-square difference[11] *(i.e., SD of difference between the 2 measurements) was 0.14 cm^2 for the systolic luminal area and 0.21 cm^2 for the diastolic area of the ascending aorta, and 0.25 cm^2 for both the systolic and diastolic areas of the descending aorta.*

Differences in the means of measurements were assessed using Student's independent t *test or, if the data were not normally distributed, Mann-Whitney U test. Correlation coefficients were calculated by the product-moment method. Numerical data are represented as mean ± SE or as median and range. A p value <0.05 was considered statistically significant.*

The Marfan group and the control children did not differ significantly in age, height, weight or calculated body surface area (Table I). Four Marfan children, but no control subject, had aortic regurgitation, the degree of which was mild in each case. The data on brachial artery blood pressure, regional aortic luminal areas and aortic distensibility are summarized in Table II. The stiffness index (median [range]) of the ascending aorta was 7.4 (2.8 to infinite) in the Marfan group and 3.1 (1.1–8.7) in the healthy control group (p <0.001). In the descending thoracic aorta, the median stiffness index measured 8.5 (3.1 to infinite) in the Marfan children and 4.0 (1.2 to 9.5) in the healthy control group (p <0.001).

Eight Marfan patients (33%) had an abnormally low distensibility in the ascending aorta (below the range in healthy children). Compared with the remaining patients, they were slightly but nonsignificantly older (12.0 ± 1.5 vs 9.7 ± 1.0 years; p = 0.219) and had a larger diastolic luminal size of the ascending aorta normalized to body area (3.6 ± 0.2 vs 2.9 ± 0.1 cm^2/m^2; p = 0.020). Patients with the sporadic form of the disease (n = 6; mean age 11.0 ± 1.3 years) had a lower distensibility than those with positive family history (n = 18; mean age 10.0 ± 1.1 years) (0.002 ± 0.001 vs 0.004 ± 0.001 mm Hg^{-1}; p = 0.03). The luminal size of the ascending aorta measured 3.7 ± 0.2 cm^2/m^2 in the former group and 3.0 ± 0.1 cm^2/m^2 in the latter (p = 0.037). Overall, a linear inverse relation was found between the distensibility and luminal size of the ascending aorta in both the Marfan (r = −0.55; p = 0.005) and healthy control (r = −0.47, p = 0.038) groups.

TABLE II Brachial Artery Blood Pressure, and Luminal Size and Distensibility of the Thoracic Aorta in Children with the Marfan Syndrome and in Healthy Control Subjects

Measurement	Patients (n = 24)	Control Subjects (n = 20)	p Value*
Brachial artery			
Systolic pressure (mm Hg)	104 ± 2	104 ± 2	0.80
Diastolic pressure (mm Hg)	63 ± 2	68 ± 2	0.02
Pulse pressure (mm Hg)	41 ± 1	36 ± 1	0.02
Ascending thoracic aorta			
Luminal area (cm^2/m^2)†	3.2 ± 0.1	2.5 ± 0.1	0.001
Systolic area change			
Absolute (cm^2)	0.6 ± 0.1	1.0 ± 0.1	<0.001
Relative (%)‡	14 ± 2	34 ± 4	<0.001
Distensibility (mm Hg^{-1})	0.004 ± 0.001	0.010 ± 0.001	<0.001
Descending thoracic aorta			
Luminal area (cm^2/m^2)†	1.8 ± 0.1	1.4 ± 0.1	<0.001
Systolic area change			
Absolute (cm^2)	0.2 ± 0.05	0.5 ± 0.1	0.001
Relative (%)‡	10 ± 2	25 ± 4	<0.001
Distensibility (mm Hg^{-1})	0.003 ± 0.001	0.007 ± 0.001	0.001

*Student's *t* test.
†Luminal areas of ascending and descending thoracic aorta were measured at end-diastole and normalized to body surface area.
‡Relative area change = absolute change as percentage of diastolic luminal area.
Data are mean ± SE.

The present data indicate an early and widespread impairment of aortic distensibility in the Marfan syndrome. These findings in children are in close agreement with the recent ultrasound study of adult Marfan patients by Hirata et al[4] showing reduced distensibility, and increased stiffness index and pulse-wave velocity in the aorta. Altogether these data fit well with the disruption and loss of elastic tissue found at postmortem or in surgical samples of the aortic tunica media.[1] The scaffolding for the elastic lamellae in the aortic wall is provided by microfibrillar fibers rich in fibrillin, a deficiency of which may be the ultimate cause of the dilatation and stiffening of the Marfan aorta.[2]

Despite the notoriety of aortic involvement in the Marfan syndrome, little attention was given to aortic distensibility before the study by Hirata et al[4] and the present investigation. Yin et al[12] measured total arterial compliance in 6 adult patients by invasive means, but whether the compliance was normal remained unknown because the study was uncontrolled. However, the investigators thought that aortic stiffness was increased, because the impedance of the proximal aorta appeared normal notwithstanding dilatation. Child et al[13] used Doppler ultrasound to measure pulse-wave velocity in the

descending thoracic aorta in patients with various connective tissue diseases, including the Marfan syndrome. Their data suggested abnormally high aortic distensibility in Marfan patients. Surprising as this finding now appears, it was in keeping with the then prevailing hypothesis of a collagen abnormality as the fundamental defect in this disease. However, increased distensibility is irreconcilable with the present data, and neither is it compatible with current views of the pathogenesis of the Marfan syndrome.

MRI provides more direct information on the size and pulsation of the thoracic aorta than does any other contemporary noninvasive technique. Its usefulness in the study of aortic distensibility is well-documented,[5,14] and the method appears sufficiently sensitive to distinguish abnormal distensibility (high or low) from normal measurements. For technical reasons, the resolution and reproducibility of measuring systolic and diastolic aortic luminal aortic areas by MRI may at present be inferior to the M-mode echocardiographic method of recording aortic diameter changes during the cardiac cycle.[4] In our experience, the repeatability of MRI measurements was better for the ascending than descending segment of the thoracic aorta.

Aortic distensibility depends on the distending pressure and decreases exponentially as the pressure increases. In our study, Marfan patients and healthy children had similar systolic blood pressures, and diastolic pressure was somewhat lower in the patient group; thus, differences in distending pressure cannot explain the difference in distensibility. Furthermore, the stiffness index (which has been validated as a pressure-independent measure of aortic elastic properties)[9] also indicated a loss of distensibility in the Marfan group.

One problem in the noninvasive methods of measuring aortic distensibility is that blood pressure is recorded indirectly in the brachial artery rather than inside the aorta; although this can distort the data in patients with occlusive arterial disease, it should be of less importance in our study. Furthermore, aortic distensibility calculated from brachial artery blood pressure has been shown to closely correlate with that from direct aortic pressure.[15] Although 4 of our patients had aortic valve regurgitation, the degree of leakage was mild and diastolic blood pressure was normal in each.

The impaired distensibility of the Marfan aorta may have certain hemodynamic consequences in addition to being of pathophysiologic interest. Poor aortic distensibility reduces the elastic forces necessary for the steady diastolic forward flow of blood in the arteries and capillaries, and also increases left ventricular afterload,[16] thus adding to the risk of heart failure with or perhaps even without valvular regurgitation. Whether knowing the aortic distensibility could help the individual prognostic assessment cannot be answered at present. In regard to the risk of aortic dissection, the echocardiographic width of the aortic root is currently considered most predictive. However, intimal tears occur even in the absence of massive aortic root dilatation, and therefore, it should be worthwhile to examine whether the information provided by MRI pertaining to the size and pulsation of the entire thoracic aorta can improve the prediction of risk.

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Cardiac Dysrhythmias Before and After Balloon Aortic Valvuloplasty in Children

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Recent reports document the success of balloon aortic valvuloplasty (BAV) in children with congenital aortic stenosis.[1] Conduction system abnormalities including severe bradycardia,[2] prolongation of the corrected QT interval[3] and ventricular arrhythmias,[1,4] have been reported during and after BAV. There have been no reports documenting the frequency of dysrhythmias both immediately before and after BAV. This study assesses rhythm abnormalities by Holter monitor recordings before and after BAV in children.

The study group consisted of 12 patients with aortic stenosis who underwent BAV between May 1987 and March 1990. Three of the 12 patients also had coarctation of the aorta, including 1 patient with Shone's complex. Patients ranged in age from 4 days to 15 years (mean 6.4 years). The mean peak systolic left ventricular to aortic pressure gradient decreased from 70 mm Hg (range 50 to 100) before to 31 mm Hg (range 4 to 57) after BAV ($p < 0.001$). The mean balloon diameter used was 108% of the annulus size (range 92 to 122%).

Two Holter monitor recordings were obtained in each patient. The first recording was completed before the catheterization. The second recording was started when the patient arrived in the intensive care unit after the catheterization. The mean duration of Holter monitoring was 18 hours (median 20, range 6 to 25) after BAV and 19 hours (median 21, range 4 to 26) after BAV.

Two of the 12 patients developed dysrhythmias during cardiac catheterization. Overdrive pacing successfully converted atrial flutter to sinus rhythm in patient 8 (Table I). Complete atrioventricular block developed in patient 11 at the time of balloon inflation. During temporary transvenous pacing, the rhythm reverted to second-degree atrioventricular block and then to sinus rhythm within 1 hour. Both patients were in normal sinus rhythm on admission to the intensive care unit after BAV. None of the patients had symptoms related to dysrhythmias or received antiarrhythmic therapy during the monitoring periods.

Premature atrial contractions occurred frequently both before (33%) and after (50%) BAV. The maximal recorded number of premature atrial contractions was 66 in 19 hours. The maximal number of premature atrial contractions per hour was 24 before and 17 after BAV. Patient 3 had a single 5-beat run of supraventricular tachycardia before and patient 12 had a single 3-beat run of supraventricular tachycardia after BAV.

Uniform ventricular premature complexes were common before (58%) and after (75%) BAV (Table I). There was no consistent trend in the number of ventricular premature complexes after BAV. The maximal number of ventricular premature contractions per hour was 88 before and 15 after BAV. The number of ventricular premature complexes increased in patient 3 from 130 before to 313 after BAV. Patient 5 had 5 multiform ventricular premature complexes after BAV. Ventricular couplets were recorded in 5 of 12 patients. The maximal number of couplets was 4 (patient 3). For the group, there was no apparent increase in the number of ventricular couplets after BAV. Short episodes of nonsustained ventricular tachycardia occurred in 3 of 12 patients. Before BAV patient 10 had 4 runs of nonsustained ventricular tachycardia, with a maximal length of 10 beats. However, there was no ventricular ectopic activity after BAV. Patient 3 had 3- and 5-beat episodes of nonsustained ventricular tachycardia after BAV. Patient 9 had a single 3-beat run of ventricular tachycardia before BAV. The patient who developed atrial flutter during the catheterization (patient 8) had only occasional ventricular premature complexes during both Holter monitor recordings. The patient who had transient atrioventricular block (patient 11) was in normal sinus rhythm for the entire duration of Holter monitoring.

Ventricular arrhythmias are common in patients with severe aortic stenosis.[5] The sudden death rate for children with aortic stenosis is 0.9%/year.[6] Weesner[4] recently reported 4 patients with Holter monitor findings of nonsustained ventricular tachycardia and frequent ventricular premature complexes after BAV, but Holter monitor recordings before BAV were not done. The natural history

TABLE I Ventricular Ectopy Before and After Balloon Aortic Valvuloplasty

	Before BAV			After BAV		
Pt.	VPC	Max. VPC/Hour	Complex Ectopy	VPC	Max. VPC/Hour	Complex Ectopy
1	1,200	50	1 VPr	168	7	3 VPr
2	0	0	0	10	2	2 VPr
3	123	14	4 VPr, VT (3)	313	—	4 VPr, 2 VT (3,5)
4	1	1	0	33	11	0
5	0	0	0	5	2	Multiform VPC
6	0	0	0	13	3	0
7	18	8	0	15	4	0
8	10	4	0	16	15	0
9	117	88	2 VPr	0	0	0
10	3	3	4 VT (max, 10)	0	0	0
11	0	0	0	0	0	0
12	0	0	0	10	3	1 VPr

BAV = balloon aortic valvuloplasty; Max. = maximum; VPC = ventricular premature contraction; VPr = ventricular pair; VT = ventricular tachycardia; 2 VT (3,5) = 2 episodes of VT lasting 3 and 5 beats each.

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of severe aortic stenosis supports careful monitoring before and after BAV. Although 2 of our 12 patients developed significant arrhythmias during BAV, our study, although limited in size, provides no evidence for a causal relation between BAV and the development of clinically significant dysrhythmias during the 24-hour period after the procedure.

In summary, atrial and ventricular dysrhythmias occur frequently in children with severe aortic stenosis both before and after BAV. Although none of the patients we report had symptoms related to the dysrhythmias noted, careful monitoring after BAV is warranted.

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Histopathologic and Angiographic Analysis of Coronary Artery Morphology Six Months After Triple Artery Angioplasty

Germano DiSciascio, MD, Danna E. Johnson, MD, and Michael J. Cowley, MD

Coronary morphology after percutaneous transluminal coronary angioplasty (PTCA) has been described in autopsy reports early after a successful or unsuccessful procedure or late after PTCA in patients with restenosis.[1-4] Opportunities for in vivo histologic examination of the chronic healed dilatation site in humans are rare. We describe angiographic and histopathologic correlations from the explanted heart of a patient who had 3-vessel PTCA and underwent cardiac transplantation 6 months later because of refractory congestive heart failure.

A 53-year-old man with unstable angina was referred for cardiac catheterization. Severe left ventricular dysfunction with ejection fraction of 22%, and 3-vessel disease with significant stenosis in the proximal anterior descending (LAD) and left circumflex (LC) arteries and diffuse narrowing of the right coronary artery were diagnosed (Figure 1, a and b). PTCA of LAD, LC and right coronary arteries was performed as a staged procedure during the same hospitalization (Figure 1, c and d). After discharge the patient had no angina. Angiography at 3 months revealed continued patency of all 3 dilated vessels (Figure 2a and 4a): There was an ectatic segment in the proximal LAD artery; the LC artery had luminal irregularity but no restenosis; the right coronary artery was widely patent and had a saccular outpouching in the midportion proximal to a narrowing of 60 to 70%; left ventricular ejection fraction was 20%. The patient had progressive deterioration of left ventricular function and underwent cardiac transplantation 6 months after initial angioplasty. At gross examination the resected heart weighed 295 g; serial cross sections of the 3 major epicardial coronary arteries were done. The region of angioplasty

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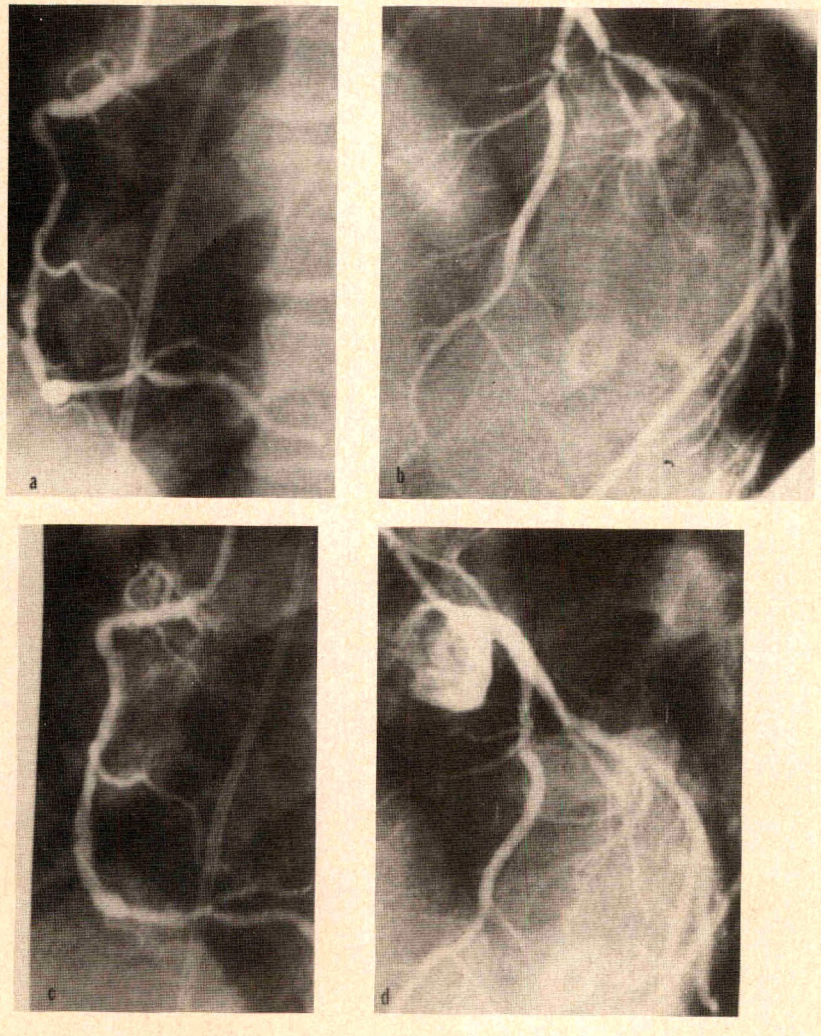


FIGURE 1. ***a and b,*** **coronary angiography before angioplasty revealing severe 3-vessel coronary disease.** ***c and d,*** **after angioplasty, there is good improvement of lumen diameter at all dilated sites, with evident tears along the right coronary artery and in the left anterior descending dilated segments.**

within the mid LC artery could not be studied because it had not been removed from the heart at surgery. At the dilated segment within the proximal LAD the underlying media was attenuated and, in places, was completely replaced by fibrous tissue. The PTCA site was clearly visible as a large radially oriented through-and-through split within the intima, with limited lateral extension within the media or along the internal elastic lamina (Figure 2, b and c). The 2 cut ends of the intima were widely separated from each other; however, the cracks and crevices produced by PTCA had been completely filled in by a highly cellular, loosely collagenous tissue rich in acid mucopolysaccharides (Figure 3). The haphazardly arranged spindle-shaped cells within this tissue had the appearance of smooth muscle cells. This hyperplastic connective tissue did not substantially impinge on the luminal area. Also, the residual artery wall seemed to bulge outward slightly at the angioplasty site suggesting that some stretching of the wall may have occurred in addition to intimal disruption. The microscopic appearance at the 2 regions of dilatation within the right coronary artery was similar to the LAD, demonstrating intimal and medial splits with repairs of the defects by proliferation of cellular, slightly fibrous connective tissue (Figure 4, b and c). The original plaques within this artery exhibited greater lipid and calcium content than those within the LAD.

Most pathologic studies of coronary artery morphology after PTCA describe patients who died as a com-

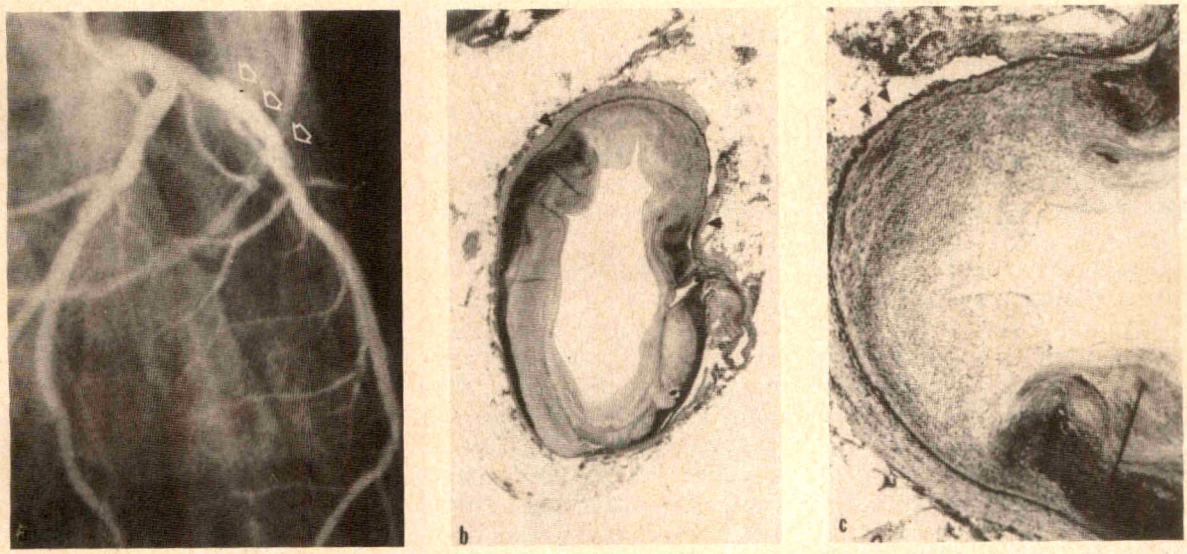


FIGURE 2. ***a,*** **follow-up angiography reveals ectatic proximal left anterior descending segment, with no evidence of restenosis in left anterior descending or circumflex arteries.** ***b,*** **left anterior descending angioplasty site, corresponding to the ectatic segment on angiogram. A tear in the plaque has created large gap** ***(between arrows)*** **which healed by intimal hyperplasia. Stretching of the external elastic membrane has produced persistent outward bulging of the wall in the region of the split.** ***c,*** **same site as in** ***b.*** **The split passes through the intima and media, leaving the adventitia intact** ***(arrows).*** **(Elastic van Gieson. Magnification:** ***b*** **× 5,** ***c*** **× 16.)**

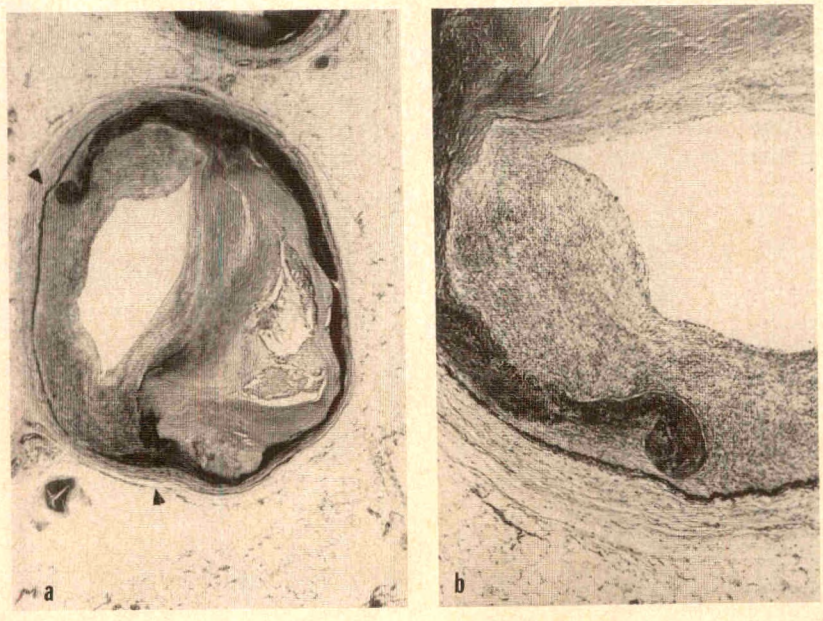


FIGURE 3. ***a,*** **angioplasty site of left anterior descending artery distal to the ectatic segment. An eccentric, calcified plaque has been widely separated where the plaque meets the thinner, disease-free wall** ***(between arrows).*** **Neointimal hyperplasia has healed the split and circumferentially coats the luminal aspects of the artery.** ***b,*** **same site as in** ***a.*** **Intimal hyperplasia is more cellular and less fibrous than the residual atherosclerotic plaque. (Elastic van Gieson. Magnification:** ***a*** **× 5,** ***b*** **× 16; reduced by 30%.)**

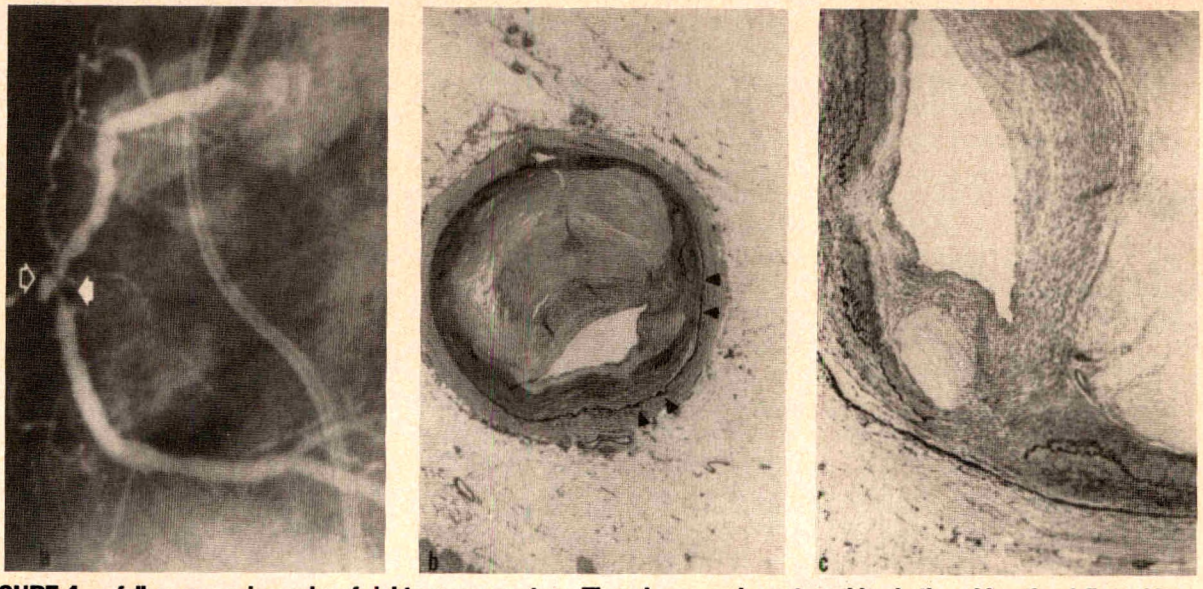


FIGURE 4. ***a,*** **follow-up angiography of right coronary artery. There is a saccular outpouching in the midportion followed by a partial restenosis.** ***b and c,*** **angioplasty site in right coronary artery, corresponding to partial restenosis distal to saccular pouch. A calcified, eccentric plaque shows 2 small, shallow splits within the intimal elastic lamina, filled in by smooth muscle cell proliferation** ***(arrows).*** **The severity of narrowing is due to intimal hyperplasia as well as the absence of extensive splitting of the media and stretching of the vessel wall (Elastic van Gieson. Magnification:** ***a*** **× 5,** ***b*** **× 16.)**

plication of the procedure, of cardiac causes early after it, or of restenosis.

This case is singular in that it represents an antemortem examination of coronary arteries in the chronic healing phase after angioplasty. The most evident sign of previous balloon-induced changes were radial intimal tears, with partial extension into the media and disruption of the internal elastic lamina. The tears were located at the nondiseased segment of the vessel. The external elastic membrane was intact at all dilated sites, and it appears that, before fibrocellular proliferation occurred, the arterial wall integrity was maintained by the outer media and adventitia. This indicates that balloon dilatation, while sparing the outer layers of the coronary artery, can cause a thinning of the vessel wall due to medial disruption, which may subsequently lead to ectasia. Intimal and medial splits were repaired by proliferation of cellular elements and fibrous connective tissue that filled the cracks but did not impinge significantly on the lumen. The right coronary artery dilated sites had a similar appearance to the LAD, although some lumen narrowing was observed: this correlates with the angiographic appearance and may be due to the higher lipid and calcium contents of the right coronary plaque, which has been associated with less favorable PTCA outcome.[5] From this study, the difference between physiologic healing and restenosis after PTCA appears to be quantitative rather than qualitative, with the clinical manifestations of the local vascular response depending on the magnitude of fibrocellular proliferation, the absolute vessel size, the severity, rigidity and composition of the underlying plaque and dynamic factors.

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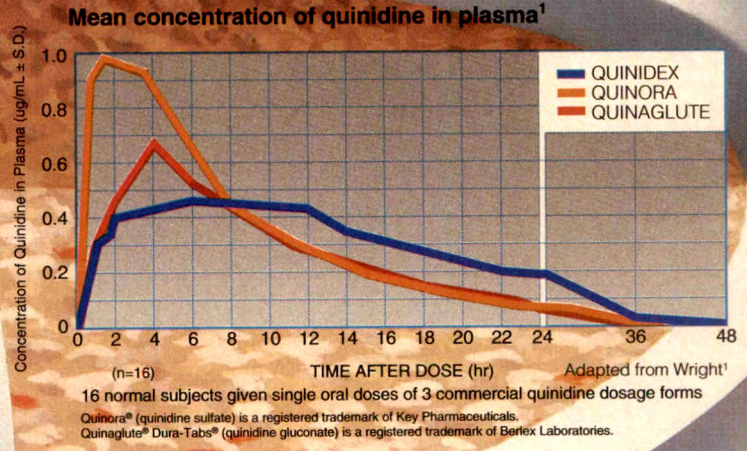
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Warnings: In the treatment of atrial flutter, reversion to sinus rhythm may be preceded by a progressive reduction in the degree of A-V block to a 1:1 ratio, resulting in an extremely rapid ventricular rate. This possible hazard may be reduced by digitalization prior to administration of quinidine.

Reports in the literature indicate that serum concentrations of digoxin may increase and may even double when quinidine is administered concurrently. Patients on concomitant therapy should be carefully monitored for digitalis toxicity. Reduction of digoxin dosage may have to be considered.

Manifestations of quinidine cardiotoxicity such as excessive prolongation of the QT interval, widening of the QRS complex and ventricular tachyarrhythmias mandate immediate discontinuation of the drug and/or close clinical and electrocardiographic monitoring.

In susceptible individuals, such as those with marginally compensated cardiovascular disease, quinidine may produce clinically important depression of cardiac function manifested by hypotension, bradycardia, or heartblock. Quinidine therapy should be carefully monitored in such individuals.

Quinidine should be used with extreme caution in patients with incomplete AV block since complete AV block and asystole may be produced. Quinidine may cause abnormalities of cardiac rhythm in digitalized patients and therefore should be used with caution in the presence of digitalis intoxication.

Quinidine should be used with caution in patients exhibiting renal, cardiac or hepatic insufficiency because of potential accumulation of quinidine in serum, leading to toxicity.

Patients taking quinidine occasionally have syncopal episodes which usually result from ventricular tachycardia or fibrillation. This syndrome has not been shown to be related to dose or serum levels. Syncopal episodes frequently terminate spontaneously or in response to treatment, but sometimes are fatal.

Cases of hepatotoxicity, including granulomatous hepatitis, due to quinidine hypersensitivity have been reported. Unexplained fever and/or elevation of hepatic enzymes, particularly in the early stages of therapy, warrant consideration of possible hepatotoxicity. Monitoring liver function during the first 4–8 weeks should be considered. Cessation of quinidine in these cases usually results in the disappearance of toxicity.

Precautions: *General*—All the precautions applying to regular quinidine therapy apply to this product. Hypersensitivity or anaphylactoid reactions to quinidine, although rare, should be considered, especially during the first weeks of therapy. Hospitalization for close clinical observation, electrocardiographic monitoring, and determination of serum quinidine levels are indicated when large doses of quinidine are used or with patients who present an increased risk.

Information for Patients—As with all solid dosage medications, Quinidex Extentabs should be taken with an adequate amount of fluid, preferably with the patient in an upright position to facilitate swallowing. They should be swallowed whole in order to preserve the controlled-release mechanism.

Laboratory Tests—Periodic blood counts and liver and kidney function tests should be performed during long-term therapy; the drug should be discontinued if blood dyscrasias or evidence of hepatic or renal dysfunction occurs.

Drug Interactions

Drug	Effect
Quinidine with anticholinergic drugs	Additive vagolytic effect
Quinidine with cholinergic drugs	Antagonism of cholinergic effects
Quinidine with carbonic anhydrase inhibitors, sodium bicarbonate, thiazide diuretics	Alkalinization of urine resulting in decreased excretion of quinidine
Quinidine with coumarin anticoagulants	Reduction of clotting factor concentrations
Quinidine with tubocurare, succinylcholine and decamethonium	Potentiation of neuromuscular blockade
Quinidine with phenothiazines and reserpine	Additive cardiac depressive effects
Quinidine with hepatic enzyme-inducing drugs (phenobarbital, phenytoin, rifampin)	Decreased plasma half-life of quinidine
Quinidine with digoxin	Increased serum concentration of digoxin (See Warnings)
Quinidine with amiodarone	Increased serum concentration of quinidine
Quinidine with cimetidine	Prolonged quinidine half-life and an increase in serum quinidine level
Quinidine with ranitidine	Premature ventricular contractions and/or bigeminy
Quinidine with verapamil	Increased quinidine half-life and an increase in serum quinidine level; potential hypotensive reactions
Quinidine with nifedipine	Decreased serum concentrations of quinidine

Carcinogenesis: Studies in animals have not been performed to evaluate the carcinogenic potential of quinidine.

Pregnancy, Teratogenic Effects: Pregnancy Category C. Animal reproduction studies have not been conducted with quinidine. There are no adequate and well-controlled studies in pregnant women. Quinidex Extentabs should be administered to a pregnant woman only if clearly indicated.

Nonteratogenic Effects: Like quinine, quinidine has been reported to have oxytocic properties. The significance of this property in the clinical setting has not been established.

Labor and Delivery—There is no known use for Quinidex Extentabs in labor and delivery. However, quinidine has been reported to have oxytocic properties. The significance of this property in the clinical setting has not been established.

Nursing Mothers—Because of passage of the drug into breast milk, caution should be exercised when Quinidex Extentabs are administered to a nursing woman.

Pediatric Use—There are no adequate and well-controlled studies establishing the safety and effectiveness of Quinidex Extentabs in children.

Adverse Reactions: Symptoms of cinchonism, such as ringing in the ears, loss of hearing, dizziness, lightheadedness, headache, nausea, and/or disturbed vision may appear in sensitive patients after a single dose of the drug. The most frequently encountered side effects to quinidine are gastrointestinal.

Gastrointestinal—Nausea, vomiting, abdominal pain, diarrhea, anorexia, granulomatous hepatitis (which may be preceded by fever), esophagitis.

Cardiovascular—Ventricular extrasystoles occurring at a rate of one or more every 6 normal beats; widening of the QRS complex and prolonged QT interval; complete A-V block; ventricular tachycardia and fibrillation; ventricular flutter; torsade de pointes; arterial embolism; hypotension; syncope.

Central Nervous System—Headache, vertigo, apprehension, excitement, confusion, delirium, dementia, ataxia, depression.

Ophthalmologic and Otologic—Disturbed hearing (tinnitus, decreased auditory acuity), disturbed vision (mydriasis, blurred vision, disturbed color perception, photophobia, diplopia, night blindness, scotomata), optic neuritis, reduced visual field.

Dermatologic—Cutaneous flushing with intense pruritus, photosensitivity, urticaria, rash, eczema, exfoliative eruptions, psoriasis, abnormalities of pigmentation.

Hypersensitivity—Angioedema, acute asthmatic episode, vascular collapse, respiratory arrest, hepatotoxicity, granulomatous hepatitis (See Warnings), purpura, vasculitis.

Hematologic—Thrombocytopenia, thrombocytopenic purpura, agranulocytosis, acute hemolytic anemia, hypoprothrombinemia, leukocytosis, shift to left in WBC differential neutropenia.

Immunologic—Systemic lupus erythematosus, lupus nephritis.

Miscellaneous—Fever, increase in serum skeletal muscle creatine phosphokinase, arthralgia, myalgia.

Rev. October 1987

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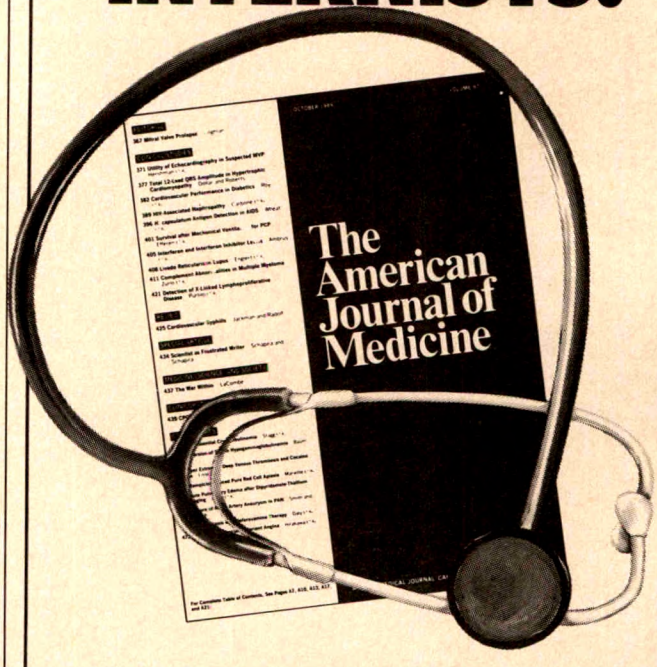
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Successful Treatment of Medically Refractory Ventricular Fibrillation with Emergency Cardiopulmonary Bypass in an Adolescent with Corrected Complex Congenital Heart Disease

Yung R. Lau, MD, Paul C. Gillette, MD, Christopher L. Case, MD, Alfred Stammers, BS, CCP, John Kratz, MD, and Barry Davis, MD

Whereas emergency cardiopulmonary bypass has become widely used in the adult population for refractory cardiac arrest,[1] there are no reported cases of its use in a pediatric patient. We report a case of an adolescent with corrected complex congenital heart disease who survived medically refractory ventricular arrhythmias by being placed on cardiopulmonary bypass.

S.M., a 16-year-old boy with d-transposition of the great arteries, was corrected with an atrial switch at 15 months of age. Five years postoperatively, he was noted to have sick sinus syndrome and a pacemaker was placed. He then had syncopal episodes which were believed secondary to atrial flutter. Recently, the atrial flutter had become almost incessant and difficult to control medically. An electrocardiogram showed atrial flutter with variable atrioventricular block. An echocardiogram revealed an enlarged right ventricle with poor contractility. An invasive electrophysiologic study was believed necessary to study additional possible mechanisms of his syncope and to overdrive his atrial flutter. After receiving a dose of ketamine intramuscularly, a 7Fr sheath was inserted into his left femoral vein. Soon after the guidewire and dilator had been removed from the sheath, he developed monomorphic ventricular tachycardia which rapidly degenerated to ventricular fibrillation. Efforts to convert his ventricular fibrillation with direct current (9 attempts of 2 J/kg) and pharmacologic agents resulted in conversion to sinus rhythm for 2 to 4 beats only.

The cardiovascular surgeons exchanged the left femoral arterial line, which had been placed shortly after cardiac arrest, and the venous line for two 20 gauge percutaneous cannulas (Research Medical, Inc., Midvalle, Utah). The bypass circuit consisting of a centrifugal pump (Bio-Medicus, Inc., Eden Prairie, Minnesota), a hollow fiber membrane oxygenator (Maxima, Medtronic Cardiopulmonary, Anaheim, California) and a heater/cooler (Biocal, Biomedicus, Inc., Eden Prairie, Minnesota) was prepared, and 41 minutes after his cardiac arrest the patient was placed on cardiopulmonary bypass. The blood flow was adjusted to achieve a cardiac index between 1.6 liters/min/m^2 (2.3 ml/min) and 2.4 liters/min/m^2 (3.6 ml/min), the blender was set at an oxygen concentration of 100%, and the sweep rate was adjusted to maintain arterial partial pressure of carbon dioxide at 40 mm Hg. His rhythm finally converted to a paced ventricular rhythm on a lidocaine drip and he was weaned off cardiopulmonary bypass. Cardiopulmonary bypass support had totaled 3 hours and 54 minutes. He remained in the hospital for 4 weeks until control of his ventricular arrhythmia (<1% ventricular ectopy by holter) was achieved with amiodarone and procainimide. However, his atrial flutter remained almost incessant. By examination, no neurologic injury was incurred during his extensive resuscitation. Four weeks after his cardiac arrest, he was discharged. His parents have subsequently refused another electrophysiologic study.

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The use of emergency cardiopulmonary bypass has become accepted in the adult population with reported survival ranging from 4 to 64%.[1] However, there have been no reported cases of its use in the pediatric population.

Serious arrhythmias are part of the natural history in a subpopulation of surgically corrected congenital heart lesions. In a patient who has undergone the Mustard procedure, these arrhythmias have typically been supraventricular (i.e., sick sinus syndrome, atrial flutter).[2] However, some investigators[3] have postulated the importance of ventricular arrhythmias in this population. This case illustrates that these patients have the capacity to develop ventricular arrhythmias with minimal provocation. Indeed, this patient's previous syncopal episodes could have been secondary to a ventricular arrhythmia rather than the presumed atrial flutter.

In anticipation of just such a labile patient, a protocol using emergency cardiopulmonary bypass for treatment of pediatric patients in cardiac arrest had been previously established at our institution. In addition, our catheterization laboratory was stocked with materials needed for placing a child weighing as little as 10 kg on cardiopulmonary bypass.

Another treatment modality that has been successful for treating refractory ventricular fibrillation is intracardiac defibrillation.[4] This was not attempted because transthoracic defibrillation had successfully converted the ventricular fibrillation though only temporarily.

Because of the potential for refractory arrhythmias in patients with surgically corrected congenital heart disease, it would seem advisable for catheterization laboratories that perform hemodynamic and electrophysiologic studies on these patients to develop a protocol for emergency cardiopulmonary bypass at their institution. This case demonstrates that the use of emergency cardiopulmonary bypass can be an extreme yet effective therapy for refractory arrhythmias in the pediatric population.

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Intrapericardial Pheochromocytoma

Thomas L. Rosamond, MD, Mitchell S. Hamburg, MD, James L. Vacek, MD, and A. Michael Borkon, MD

Intrapericardial pheochromocytoma is a rare diagnosis.[1–7] The first case description[1] was published in 1974, and by 1983 only 3 such tumors had been reported.[2] At present, <10 cases have been documented in the world's literature. The diagnosis and localization of these tumors (as is true of other extra-adrenal pheochromocytomas) are often difficult. The recent development of iodine-131 metaiodobenzylguanidine nuclear scanning has assisted in diagnosis and localization of these neoplasms,[1,3,5] whereas computerized tomographic studies or nuclear magnetic resonance imaging have assisted in more precise localization.[5,6] At times, the diagnosis and localization of this tumor remains problematic. We report a case where transesophageal echocardiography provided unique information that resulted in the diagnosis of an intrapericardial pheochromocytoma.

A 46-year-old white woman had been found to have systemic hypertension at age 30 years. Since age 41, she had had 3 episodes of increased blood pressure and an irregular heartbeat during induction of anesthesia. At age 40, she had a left nephrectomy for pyelonephritis, at age 41, a hysterectomy, and at age 44, a cholecystectomy.

An initial evaluation by her family physician in 1989 revealed increased 24-hour urinary excretion of metanephrine (3.86 and 1.79 mg on 2 recordings, with a normal range of up to 1.3 mg/24 hours). Vanillylmandelic acid was normal at 4.5 mg/24 hours, whereas total urinary catecholamines were increased to 228 μg/24 hours (normal range up to 150). Plasma norepinephrine measured 2,026 pg/ml (normal 0 to 600), and dopamine 8,154 pg/ml (normal 80 to 400). Plasma epinephrine levels were within normal limits. A computerized tomogram of the abdomen was obtained and interpreted to show no abnormalities, with the exception of the absence of the left kidney. The patient was receiving no medications at the time of this initial evaluation.

The patient was reevaluated after receiving Tenex (2 mg orally) twice a day for blood pressure control. Repeat computerized tomography of the abdomen, neck and chest were performed, and all were negative. A thallium myocardial perfusion study was also performed and interpreted to show no evidence of myocardial ischemia. A 24-hour urinary metanephrine collection was repeated and found to be normal, measuring 76 μg/24 hours (normal 44 to 300). However, normetanephrine levels were increased, measuring 3,388 μg (normal up to 620). Urinary epinephrine secretion was within normal limits. Norepinephrine and urinary dopamine levels were slightly increased. Resting plasma catecholamines were also abnormal, with a norepinephrine level of 2,071 pg/ml, whereas plasma epinephrine and dopamine levels were within normal limits. During an episode of chest pain, the norepinephrine level was again measured and found to be increased at 3,439 pg/ml, with normal plasma epinephrine and dopamine levels.

Because the patient was receiving Xanax and Tenex therapy at the time of the assays and because of possible drug interference, these medications were stopped, the patient was administered Verapamil SR (180 mg orally) daily, and the studies were repeated. A 24-hour urinary excretion of normetanephrine was subsequently documented to be increased at 2,613 μg, with a repeat metanephrine level being within normal limits. The patient continued to have paroxysmal symptoms including spells of dizziness, near syncope, headache, flushing sensation, palpitations and chest pains.

An iodine-131 metaiodobenzylguanidine scan was performed in September 1990. The study demonstrated increased focal concentration of tracer in the right lower mediastinum. The patient's previous chest computerized axial tomography scans were reviewed in this region, but no localized mass could be detected.

At age 45 years, a transesophageal echocardiogram was obtained and revealed a localized mass within the pericardium, immediately adjacent to the heart (Figures 1 and 2). The patient was administered phenoxybenzamine (10 mg orally) 4 times daily, which was gradually increased to 20 mg four times daily. The patient was also administered propranolol (20 mg orally) 4 times daily. In November 1990, the patient

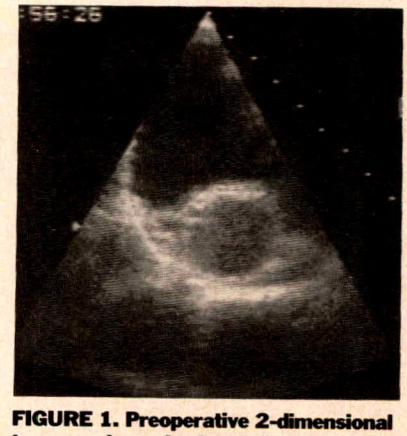


FIGURE 1. Preoperative 2-dimensional transesophageal echocardiogram indicating intrapericardial spherical mass in atrioventricular groove adjacent to tricuspid valve and right coronary artery.

From Mid America Heart Institute, and the Section of Endocrinology, St. Luke's Hospital, Kansas City, Missouri. Dr. Rosamond's current address is: Mid-America Cardiology Associates, 4321 Washington, Suite 4000, Kansas City, Missouri 64111. Manuscript received January 21, 1992; revised manuscript received and accepted April 20, 1992.

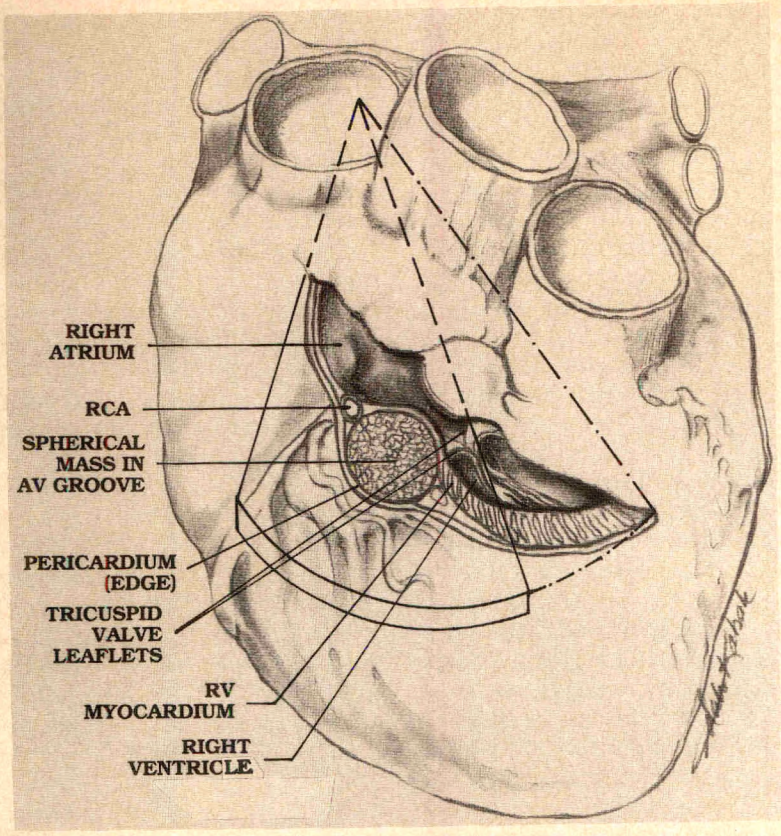


FIGURE 2. Schematic representation of transesophageal plane in Figure 1 displaying spherical mass in atrioventricular (AV) groove within pericardium and located along right coronary artery (RCA) in atrioventricular groove. RV = right ventricular.

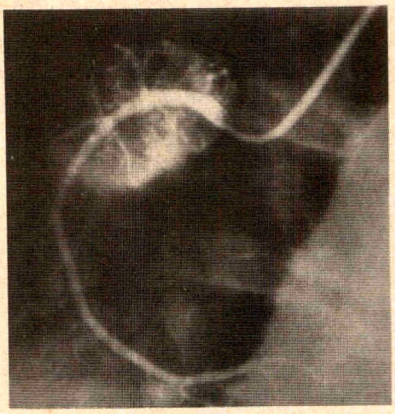


FIGURE 3. Coronary cineangiogram of right coronary artery in 45° left anterior oblique projection, with 10° of caudal angulation. Elliptical spherical mass is seen along proximal right coronary artery and derives its blood flow from proximal branch of right coronary artery.

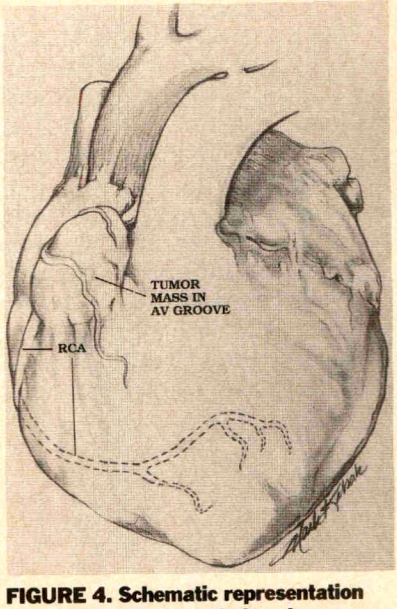


FIGURE 4. Schematic representation of position of spherical pheochromocytoma along proximal right coronary artery (RCA) corresponding to coronary angiogram in Figure 3. AV = atrioventricular.

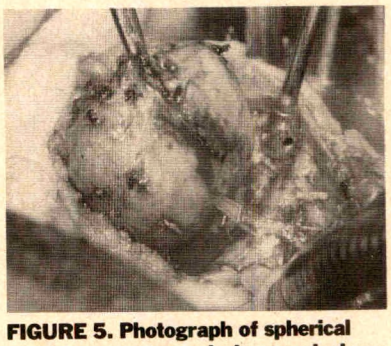


FIGURE 5. Photograph of spherical pheochromocytoma during surgical exploration of pericardium.

was studied by coronary cineangiography and right heart catheterization. Before contrast injection and to document the catecholamine-producing capability of the tumor, samples of blood were obtained from the low and high inferior vena cava, the right atrium and the main pulmonary artery. Table I displays the value for blood sampling of catecholamines. It is apparent that a large step up in plasma norepinephrine is present from the low inferior vena cava advancing through the right atrium and into the main pulmonary artery. The peak norepinephrine levels were present in the high right atrium, reaching 45,971 pg/ml (normal values 700 to 750 in the supine position). There is a paucity of epinephrine secretion by this tumor, which is compatible with the patient's clinical history. The data indicate that the venous drainage of the tumor emptied into the right atrium, confirming the cardiac origin of catecholamine production. Left ventriculography revealed mild global hypokinesia, with an ejection fraction of 45 to 50%. Coronary cineangiography revealed 3 side branches of the right coronary artery supplying a tumor (approximately 3 cm in diameter) immediately adjacent to the heart and located in the atrial ventricular groove (Figures 3 and 4). The remainder of the coronary anatomy was unremarkable. The patient was subsequently taken to the operating room, and the tumor

TABLE I Plasma Catecholamine Levels (pg/ml)

	Norepinephrine	Epinephrine	Dopamine
Low IVC	2,014	31	14
High IVC	2,053	123	21
Right atrium	45,971	141	92
Main pulmonary artery	6,296	91	53

Normal supine levels: norepinephrine 70 to 750 pg/ml; epinephrine 0 to 110 pg/ml; dopamine <30 pg/ml.
IVC = inferior vena cava.

was removed while the patient was on cardiopulmonary bypass (Figure 5).

Pathologic examination revealed a 3.4 × 2.5 × 2 cm soft ovoid specimen. The cut surface was vaguely nodular, and tan and gray in appearance. Histologically, the tumor displayed a paraganglioma pattern with rounded nests of cells surrounded by capillaries. Although the specimen was circumscribed, the tumor was not entirely encapsulated and did infiltrate some myocardial fibers at its periphery. Histologically, the capacity for metastases could not be definitely evaluated, because morphology is known to be an unreliable determinant of metastatic potential. The tumor cells were strongly positive for chromogranin, corroborating the clinical diagnosis of pheochromocytoma.

Pheochromocytomas associated with the heart are extraordinarily infrequent, particularly those located within the pericardium. To our knowledge, <10 cases of intrapericardial pheochromocytoma have been reported. The first case was not reported until 1974, and only in the past decade with advanced imaging and localization techniques has this diagnosis been obtained with greater frequency. Ninety percent of pheochromocytomas are adrenal in origin, 9% occur elsewhere in the abdomen, and only 1% occur outside the abdomen. Of all extraabdominal tumors, approximately 20% originate in the chest. If an intraabdominal site for a pheochromocytoma is not evident, the recommended next step in evaluation is iodine-131 metaiodobenzylguanidine scintigraphy.[2,4,6] This technique appears to be extremely sensitive in diagnosing the presence of extraadrenal pheochromocytomas; it is also useful in the diagnosing of intrathoracic tumors, but because of limitations in its resolving capabilities, it does not allow for precise localization of the tumor and delineation of its relation to adjacent structures. Initially, standard computerized tomography, then dynamic contrast-enhanced computerized tomography, and finally magnetic resonance imaging have been used to assist in the precise localization and definition of these tumors.[2–7] As in this case, these methods are not always definitive, and cause some expense and inconvenience for the patient. Augmentation of the diagnostic armamentarium by additional noninvasive techniques would be of considerable benefit.

Transesophageal echocardiography, however, provides a unique echocardiographic window, which excels in the visualization of the posterior surface of the heart. In the present case, tumor position and characteristics were well-defined by transesophageal echocardiography and were not delineated by transthoracic echocardiography. Transesophageal echocardiography suggested the coronary origin of this tumor's nutrient blood supply. This resulted in a very cautious approach to coronary cineangiography, given the potential for precipitating a hypertensive crisis should direct injection into the tumor's blood supply occur during coronary cineangiography.

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References: 1. *A Report of the Surgeon General: Smoking and Health*, publication 79-50066. US Department of Health, Education, and Welfare, 1979. **2.** Bouknight LG, Bouknight RR: Cocaine—a particularly addictive drug. *Postgrad Med* 1988;83(4):115-131. **3.** Derlet RW: Cocaine intoxication. *Postgrad Med* 1989;86(5):245-253. **4.** Buchanan JF: Cocaine intoxication: A review of the presentation and treatment of medical complications. *Hospital Phys* 1988;3:24-28.

Drug Abuse

You don't have to preach about it...teach about it

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MT-277

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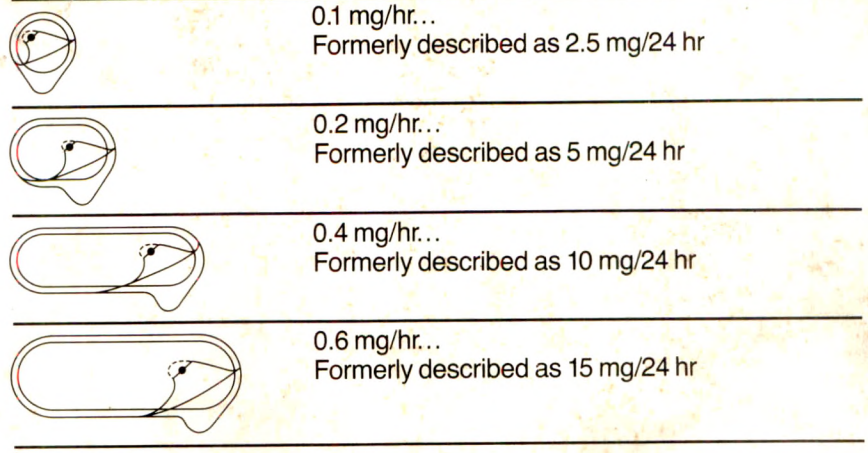
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Every Transderm-Nitro patch has the exclusive easy-open tab

Easy to apply—
Easy to remove

Available in four convenient dosages

Patches not shown actual size



Transderm-Nitro®
nitroglycerin
Transdermal Therapeutic System

Revised Dosage Information

BRIEF SUMMARY (FOR FULL PRESCRIBING INFORMATION, SEE PACKAGE INSERT)

INDICATIONS AND USAGE
This drug product has been conditionally approved by the FDA for the prevention of angina pectoris due to coronary artery disease. Tolerance to the antianginal effects of nitrates (measured by exercise stress testing) has been shown to be a major factor limiting efficacy when transdermal nitrates are used continuously for longer than 12 hours each day. The development of tolerance can be altered (prevented or attenuated) by use of a noncontinuous (intermittent) dosing schedule with a nitrate-free interval of 10-12 hours.

Controlled clinical trial data suggest that the intermittent use of nitrates is associated with decreased exercise tolerance, in comparison to placebo, during the last part of the nitrate-free interval; the clinical relevance of this observation is unknown, but the possibility of increased frequency or severity of angina during the nitrate-free interval should be considered. Further investigations of the tolerance phenomenon and best regimen are ongoing. A final evaluation of the effectiveness of the product will be announced by the FDA.

CONTRAINDICATIONS
Allergic reactions to organic nitrates are extremely rare, but they do occur. Nitroglycerin is contraindicated in patients who are allergic to it. Allergy to the adhesives used in nitroglycerin patches has also been reported, and it similarly constitutes a contraindication to the use of this product.

WARNINGS
The benefits of transdermal nitroglycerin in patients with acute myocardial infarction or congestive heart failure have not been established. If one elects to use nitroglycerin in these conditions, careful clinical or hemodynamic monitoring must be used to avoid the hazards of hypotension and tachycardia.

A cardioverter/defibrillator should not be discharged through a paddle electrode that overlies a Transderm-Nitro patch. The arcing that may be seen in this situation is harmless in itself, but it may be associated with local current concentration that can cause damage to the paddles and burns to the patient.

PRECAUTIONS
General
Severe hypotension, particularly with upright posture, may occur with even small doses of nitroglycerin. This drug should therefore be used with caution in patients who may be volume depleted or who, for whatever reason, are already hypotensive. Hypotension induced by nitroglycerin may be accompanied by paradoxical bradycardia and increased angina pectoris.

Nitrate therapy may aggravate the angina caused by hypertrophic cardiomyopathy.

As tolerance to other forms of nitroglycerin develops, the effect of sublingual nitroglycerin on exercise tolerance, although still observable, is somewhat blunted.

In industrial workers who have had long-term exposure to unknown (presumably high) doses of organic nitrates, tolerance clearly occurs. Chest pain, acute myocardial infarction, and even sudden death have occurred during temporary withdrawal of nitrates from these workers, demonstrating the existence of true physical dependence.

Several clinical trials in patients with angina pectoris have evaluated nitroglycerin regimens which incorporated a 10-12 hour nitrate-free interval. In some of these trials, an increase in the frequency of anginal attacks during the nitrate-free interval was observed in a small number of patients. In one trial, patients demonstrated decreased exercise tolerance at the end of the nitrate-free interval. Hemodynamic rebound has been observed only rarely; on the other hand, few studies were so designed that rebound, if it had occurred, would have been detected. The importance of these observations to the routine, clinical use of transdermal nitroglycerin is unknown.

Information for Patients
Daily headaches sometimes accompany treatment with nitroglycerin. In patients who get these headaches, the headaches may be a marker of the activity of the drug. Patients should resist the temptation to avoid headaches by altering the schedule of their treatment with nitroglycerin, since loss of headache may be associated with simultaneous loss of antianginal efficacy.

Treatment with nitroglycerin may be associated with lightheadedness on standing, especially just after rising from a recumbent or seated position. This effect may be more frequent in patients who have also consumed alcohol.

After normal use, there is enough residual nitroglycerin in discarded patches that they are a potential hazard to children and pets.

A patient leaflet is supplied with the systems.

Drug Interactions
The vasodilating effects of nitroglycerin may be additive with those of other vasodilators. Alcohol, in particular, has been found to exhibit additive effects of this variety.

Marked symptomatic orthostatic hypotension has been reported when calcium channel blockers and organic nitrates were used in combination. Dose adjustments of either class of agents may be necessary.

Carcinogenesis, Mutagenesis, Impairment of Fertility
No long-term animal studies have examined the carcinogenic or mutagenic potential of nitroglycerin. Nitroglycerin's effect upon reproductive capacity is similarly unknown.

Pregnancy Category C
Animal reproduction studies have not been conducted with nitroglycerin. It is also not known whether nitroglycerin can cause fetal harm when administered to a pregnant woman or whether it can affect reproductive capacity. Nitroglycerin should be given to a pregnant woman only if clearly needed.

Nursing Mothers
It is not known whether nitroglycerin is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when nitroglycerin is administered to a nursing woman.

Pediatric Use
Safety and effectiveness in children have not been established.

ADVERSE REACTIONS
Adverse reactions to nitroglycerin are generally dose-related, and almost all of these reactions are the result of nitroglycerin's activity as a vasodilator. Headache, which may be severe, is the most commonly reported side effect. Headache may be recurrent with each daily dose, especially at higher doses. Transient episodes of lightheadedness, occasionally related to blood pressure changes, may also occur. Hypotension occurs infrequently, but in some patients it may be severe enough to warrant discontinuation of therapy. Syncope, crescendo angina, and rebound hypertension have been reported but are uncommon.

Extremely rarely, ordinary doses of organic nitrates have caused methemoglobinemia in normal-seeming patients. Methemoglobinemia is so infrequent at these doses that further discussion of its diagnosis and treatment is deferred (see Overdosage).

Application-site irritation may occur but is rarely severe.

In two placebo-controlled trials of intermittent therapy with nitroglycerin patches at 0.2 to 0.8 mg/hr, the most frequent adverse reactions among 307 subjects were as follows:

	Placebo	Patch
Headache	18%	63%
Lightheadedness	4%	6%
Hypotension, and/or syncope	0%	4%
Increased angina	2%	2%

OVERDOSAGE
Hemodynamic Effects
The ill effects of nitroglycerin overdose are generally the result of nitroglycerin's capacity to induce vasodilatation, venous pooling, reduced cardiac output, and hypotension. These hemodynamic changes may have protean manifestations, including increased intracranial pressure, with any or all of persistent throbbing headache, confusion, and moderate fever; vertigo; palpitations; visual disturbances; nausea and vomiting (possibly with colic and even bloody diarrhea); syncope (especially in the upright posture); air hunger and dyspnea, later followed by reduced ventilatory effort; diaphoresis, with the skin either flushed or cold and clammy; heart block and bradycardia; paralysis; coma; seizures; and death.

Laboratory determinations of serum levels of nitroglycerin and its metabolites are not widely available, and such determinations have, in any event, no established role in the management of nitroglycerin overdose.

No data are available to suggest physiological maneuvers (e.g., maneuvers to change the pH of the urine) that might accelerate elimination of nitroglycerin and its active metabolites. Similarly, it is not known which, if any, of these substances can usefully be removed from the body by hemodialysis.

No specific antagonist to the vasodilator effects of nitroglycerin is known, and no intervention has been subject to controlled study as a therapy of nitroglycerin overdose. Because the hypotension associated with nitroglycerin overdose is the result of venodilatation and arterial hypovolemia, prudent therapy in this situation should be directed toward an increase in central fluid volume. Passive elevation of the patient's legs may be sufficient, but intravenous infusion of normal saline or similar fluid may also be necessary.

The use of epinephrine or other arterial vasoconstrictors in this setting is likely to do more harm than good.

In patients with renal disease or congestive heart failure, therapy resulting in central volume expansion is not without hazard. Treatment of nitroglycerin overdose in these patients may be subtle and difficult, and invasive monitoring may be required.

Methemoglobinemia
Nitrate ions liberated during metabolism of nitroglycerin can oxidize hemoglobin into methemoglobin. Even in patients totally without cytochrome b_5 reductase activity, however, and even assuming that the nitrate moieties of nitroglycerin are quantitatively applied to oxidation of hemoglobin, about 1 mg/kg of nitroglycerin should be required before any of these patients manifests clinically significant ($\geq$ 10%) methemoglobinemia. In patients with normal reductase function, significant production of methemoglobin should require even larger doses of nitroglycerin. In one study in which 36 patients received 2-4 weeks of continuous nitroglycerin therapy at 3.1 to 4.4 mg/hr, the average methemoglobin level measured was 0.2%; this was comparable to that observed in parallel patients who received placebo.

Notwithstanding these observations, there are case reports of significant methemoglobinemia in association with moderate overdoses of organic nitrates. None of the affected patients had been thought to be unusually susceptible.

Methemoglobin levels are available from most clinical laboratories. The diagnosis should be suspected in patients who exhibit signs of impaired oxygen delivery despite adequate cardiac output and adequate arterial pO_2. Classically, methemoglobinemic blood is described as chocolate brown, without color change on exposure to air.

When methemoglobinemia is diagnosed, the treatment of choice is methylene blue, 1-2 mg/kg intravenously.

DOSAGE AND ADMINISTRATION
The suggested starting dose is between 0.2 mg/hr*, and 0.4 mg/hr*. Doses between 0.4 mg/hr* and 0.8 mg/hr* have shown continued effectiveness for 10-12 hours daily for at least one month (the longest period studied) of intermittent administration. Although the minimum nitrate-free interval has not been defined, data show that a nitrate-free interval of 10-12 hours is sufficient (see INDICATIONS AND USAGE). Thus, an appropriate dosing schedule for nitroglycerin patches would include a daily patch-on period of 12-14 hours and a daily patch-off period of 10-12 hours.

Although some well-controlled clinical trials using exercise tolerance testing have shown maintenance of effectiveness when patches are worn continuously, the large majority of such controlled trials have shown the development of tolerance (i.e., complete loss of effect) within the first 24 hours after therapy was initiated. Dose adjustment, even to levels much higher than generally used, did not restore efficacy.

PATIENT INSTRUCTIONS FOR APPLICATION OF SYSTEM
A patient leaflet is supplied with each carton.

HOW SUPPLIED

Transderm-Nitro System*	Total Nitroglycerin in System	System Size	Carton Size
0.1 mg/hr	12.5 mg	5 cm²	30 Systems...NDC 57267-902-26
			**30 Systems...NDC 57267-902-42
			**100 Systems...NDC 57267-902-30
0.2 mg/hr	25 mg	10 cm²	30 Systems...NDC 57267-905-26
			**30 Systems...NDC 57267-905-42
			**100 Systems...NDC 57267-905-30
0.4 mg/hr	50 mg	20 cm²	30 Systems...NDC 57267-910-26
			**30 Systems...NDC 57267-910-42
			**100 Systems...NDC 57267-910-30
0.6 mg/hr	75 mg	30 cm²	30 Systems...NDC 57267-915-26
			**30 Systems...NDC 57267-915-42
			**100 Systems...NDC 57267-915-30

**Institutional Pack

*Rated release in vivo. Release rates were formerly described in terms of drug delivered per 24 hours. In these terms, the supplied Transderm-Nitro systems would be rated at 2.5 mg/24 hr (0.1 mg/hr), 5 mg/24 hr (0.2 mg/hr), 10 mg/24 hr (0.4 mg/hr), and 15 mg/24 hr (0.6 mg/hr).

Do not store above 86°F (30°C).

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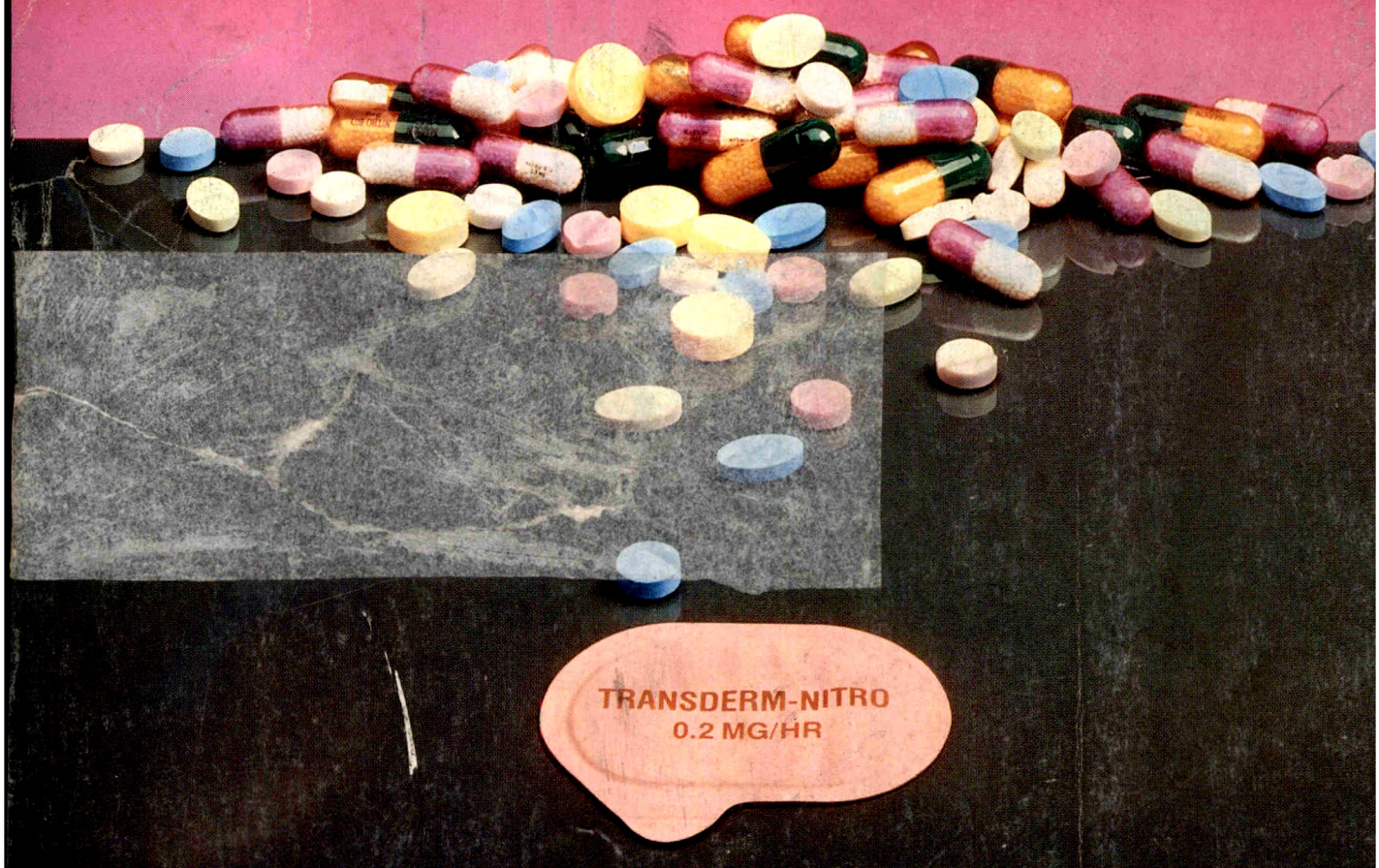
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References:
1. Brady EM, Gold OG, Rosenbach HJ. Antianginal efficacy of transdermal nitroglycerin and oral nitrates: The ACTION Study. *Cardiovasc Rev Rep*. October 1988: 40-44.

The nitrate your patients will stick with



Simple, once-daily patch application

Patient-preferred 7 to 1 for convenience compared with oral nitrates (12% had no preference, n=4,300)[1]

Easy-to-handle nonadhesive tab

As with all nitroglycerin medications, side effects may occur with Transderm-Nitro, the most common of which is headache. All transdermal nitroglycerin products are being marketed pending final evaluation of effectiveness by the FDA. Please consult brief summary of Prescribing Information on following page.

Transderm-Nitro®
nitroglycerin 0.1 mg/hr, 0.2 mg/hr, 0.4 mg/hr, 0.6 mg/hr*

Summit Pharmaceuticals
Division of CIBA–GEIGY Corporation

At the heart of nitrate compliance

*Formerly described as 2.5 mg/24 hr, 5 mg/24 hr, 10 mg/24 hr, 15 mg/24 hr.

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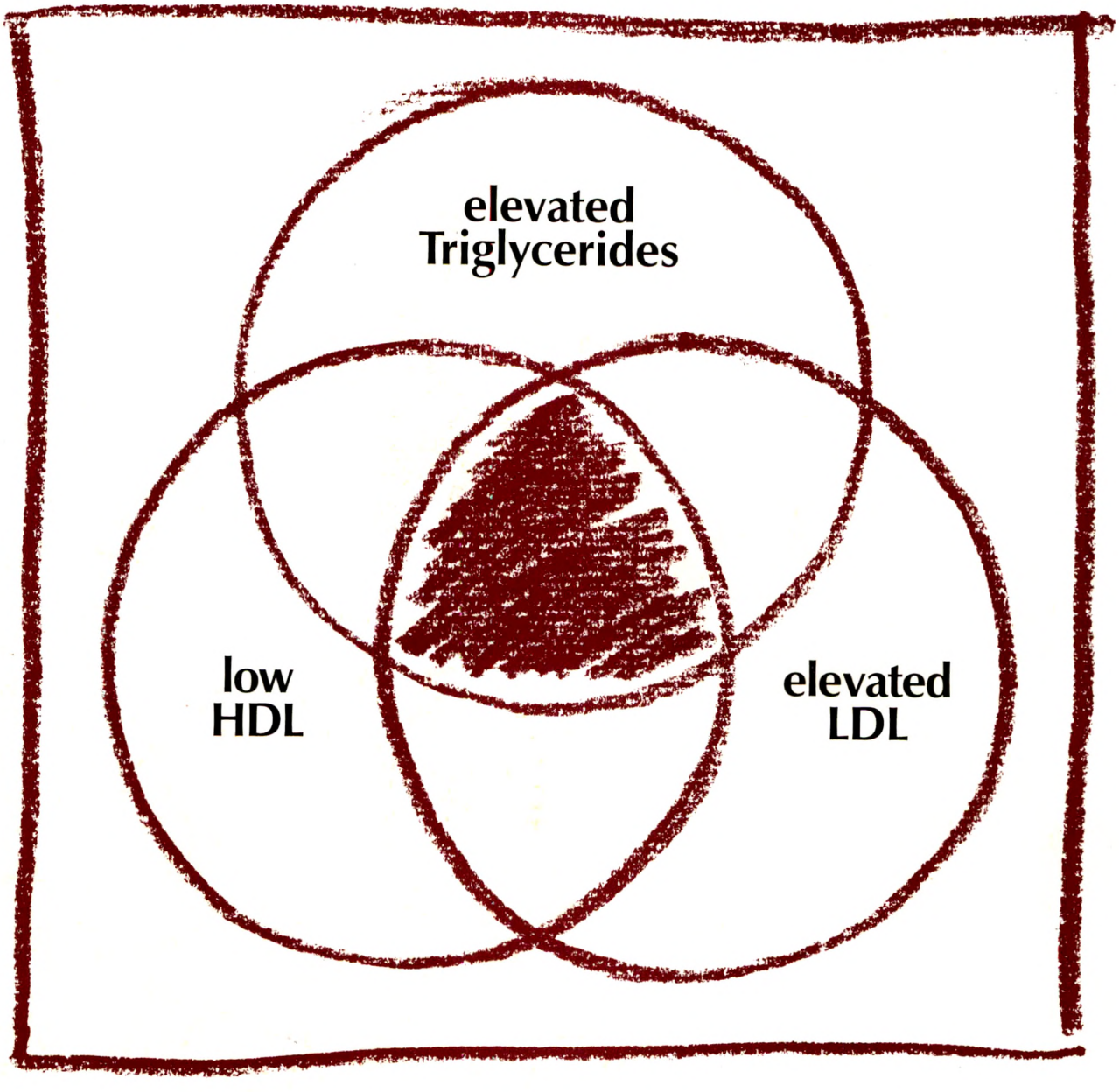
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Reduce the risk of developing CHD in patients with the triad of risk...



As an adjunct to diet, after an inadequate response to exercise, dietary therapy, weight loss and trial of other pharmacologic agents (such as bile acid sequestrants and nicotinic acid)

LOPID®

(gemfibrozil) 600-mg Tablets BID

REDUCES THE RISK OF DEVELOPING CHD
IN PATIENTS WITH THE TRIAD OF RISK

LOPID is indicated as adjunctive therapy to diet for reducing the risk of developing coronary heart disease **only** in Type IIb patients:

- Without history of or symptoms of existing coronary heart disease
- Who have had an inadequate response to weight loss, dietary therapy, exercise, and other pharmacologic agents (such as bile acid sequestrants and nicotinic acid, known to reduce LDL- and raise HDL-cholesterol)

and

- Who have the following triad of lipid abnormalities: low HDL-cholesterol levels in addition to elevated LDL-cholesterol and elevated triglycerides

In addition:

- The potential benefit of gemfibrozil in treating Type IIa patients with elevations of LDL-cholesterol only is not likely to outweigh the risks
- LOPID is not indicated for the treatment of patients with low HDL-cholesterol as their only lipid abnormality

LOPID is contraindicated in patients with hepatic or severe renal dysfunction, including primary biliary cirrhosis, preexisting gallbladder disease, or hypersensitivity to gemfibrozil

LOPID may increase cholesterol secretion into the bile, leading to cholelithiasis

Caution should be exercised when anticoagulants are given in conjunction with LOPID

Please see last page of this advertisement for brief summary of prescribing information.

PARKE-DAVIS

BOOTS PHARMACEUTICALS

PARKE-DAVIS Division of Warner-Lambert Company, Morris Plains, New Jersey 07950

Before prescribing, please see full prescribing information. A Brief Summary follows.

CONTRAINDICATIONS

1. Hepatic or severe renal dysfunction, including primary biliary cirrhosis.
2. Preexisting gallbladder disease (see WARNINGS).
3. Hypersensitivity to gemfibrozil.

WARNINGS

1. Because of chemical, pharmacological, and clinical similarities between gemfibrozil and clofibrate, the adverse findings with clofibrate in two large clinical studies may also apply to gemfibrozil. In the first of those studies, the Coronary Drug Project, 1000 subjects with previous myocardial infarction were treated for five years with clofibrate. There was no difference in mortality between the clofibrate-treated subjects and 3000 placebo-treated subjects, but twice as many clofibrate-treated subjects developed cholelithiasis and cholecystitis requiring surgery. In the other study, conducted by the World Health Organization (WHO), 5000 subjects without known coronary heart disease were treated with clofibrate for five years and followed one year beyond. There was a statistically significant, 44%, higher age-adjusted total mortality in the clofibrate-treated than in a comparable placebo-treated control group during the trial period. The excess mortality was due to a 33% increase in noncardiovascular causes, including malignancy, post-cholecystectomy complications, and pancreatitis. The higher risk of clofibrate-treated subjects for gallbladder disease was confirmed.

Because of the more limited size of the Helsinki Heart Study, the observed difference in mortality from any cause between the Lopid and placebo group is not statistically significantly different from the 29% excess mortality reported in the clofibrate group in the separate WHO study at the 9 year follow-up. Noncoronary heart disease related mortality showed an excess in the group originally randomized to Lopid primarily due to cancer deaths observed during the open-label extension.

During the 5 year primary prevention component of the Helsinki Heart Study mortality from any cause was 44 (2.2%) in the Lopid group and 43 (2.1%) in the placebo group; including the 3.5 year follow-up period since the trial was completed, cumulative mortality from any cause was 101 (4.9%) in the Lopid group and 83 (4.1%) in the group originally randomized to placebo (hazard ratio 1.20 in favor of placebo). Because of the more limited size of the Helsinki Heart Study, the observed difference in mortality from any cause between the Lopid and placebo groups at year-5 or at year-8.5 is not statistically significantly different from the 29% excess mortality reported in the clofibrate group in the separate WHO study at the 9 year follow-up. Noncoronary heart disease related mortality showed an excess in the group originally randomized to Lopid at the 8.5 year follow-up (65 Lopid versus 45 placebo noncoronary deaths).

The incidence of cancer (excluding basal cell carcinoma) discovered during the trial and in the 3.5 years after the trial was completed was 51 (2.5%) in both originally randomized groups. In addition, there were 16 basal cell carcinomas in the group originally randomized to Lopid and 9 in the group originally randomized to placebo ($p = 0.22$). There were 30 (1.5%) deaths attributed to cancer in the group originally randomized to Lopid and 18 (0.9%) in the group originally randomized to placebo ($p = 0.11$). Adverse outcomes, including coronary events, were higher in gemfibrozil patients in a corresponding study in men with a history of known or suspected coronary heart disease in the secondary prevention component of the Helsinki Heart Study. See CLINICAL PHARMACOLOGY section in full prescribing information which includes the following: The secondary prevention component of the Helskinki Heart Study was conducted over 5 years in parallel and at the same centers in Finland in 628 middle-aged males excluded from the primary prevention component of the Helsinki Heart Study because of a history of angina, myocardial infarction or unexplained ECG changes. The primary efficacy endpoint of the study was cardiac events (the sum of fatal and non-fatal myocardial infarctions and sudden cardiac deaths). The hazard ratio (Lopid:placebo) for cardiac events was 1.47 (95% confidence limits 0.88-2.48, p=0.14). Of the 35 patients in the Lopid group who experienced cardiac events, 12 patients suffered events after discontinuation from the study. Of the 24 patients in the placebo group with cardiac events, 4 patients suffered events after discontinuation from the study. There were 17 cardiac deaths in the Lopid group and 8 in the placebo group (hazard ratio 2.18; 95% confidence limits 0.94-5.05, p=0.06). Ten of these deaths in the Lopid group and 3 in the placebo group occurred after discontinuation from therapy. In this study of patients with known or suspected coronary heart disease, no benefit from Lopid treatment was observed in reducing cardiac events or cardiac deaths. Thus, Lopid has shown benefit only in selected dyslipidemic patients *without* suspected or established coronary heart disease. Even in patients with coronary heart disease and the triad of elevated LDL-cholesterol, elevated triglycerides, plus low HDL-cholesterol, the possible effect of Lopid on coronary events has not been adequately studied.

2. A gallstone prevalence substudy of 450 Helsinki Heart Study participants showed a trend toward a greater prevalence of gallstones during the study within the Lopid treatment group (7.5% vs 4.9% for the placebo group, a 55% excess for the gemfibrozil group). A trend toward a greater incidence of gallbladder surgery was observed for the Lopid group (17 vs 11 subjects, a 54% excess). This result did not differ statistically from the increased incidence of cholecystectomy observed in the WHO study in the group treated with clofibrate. Both clofibrate and gemfibrozil may increase cholesterol excretion into the bile leading to cholelithiasis. If cholelithiasis is suspected, gallbladder studies are indicated. Lopid therapy should be discontinued if gallstones are found.

3. Since a reduction of mortality from coronary heart disease has not been demonstrated and because liver and interstitial cell testicular tumors were increased in rats, Lopid should be administered only to those patients described in the INDICATIONS AND USAGE section. If a significant serum lipid response is not obtained, Lopid should be discontinued.

4. Concomitant Anticoagulants – Caution should be exercised when anticoagulants are given in conjunction with Lopid. The dosage of the anticoagulant should be reduced to maintain the prothrombin time at the desired level to prevent bleeding complications. Frequent prothrombin determinations are advisable until it has been definitely determined that the prothrombin level has stabilized.

5. Concomitant therapy with Lopid and Mevacor® (lovastatin) has been associated with rhabdomyolysis, markedly elevated creatine kinase (CK) levels and myoglobinuria, leading in a high proportion of cases to acute renal failure. IN VIRTUALLY ALL PATIENTS WHO HAVE HAD AN UNSATISFACTORY LIPID RESPONSE TO EITHER DRUG ALONE, ANY POTENTIAL LIPID BENEFIT OF COMBINED THERAPY WITH LOVASTATIN AND GEMFIBROZIL DOES NOT OUTWEIGH THE RISKS OF SEVERE MYOPATHY, RHABDOMYOLYSIS, AND ACUTE RENAL FAILURE (see Drug Interactions). The use of fibrates alone, including Lopid, may occasionally be associated with myositis. Patients receiving Lopid and complaining of muscle pain, tenderness, or weakness should have prompt medical evaluation for myositis, including serum creatine kinase level determination. If myositis is suspected or diagnosed, Lopid therapy should be withdrawn.

6. Cataracts – Subcapsular bilateral cataracts occurred in 10%, and unilateral in 6.3% of male rats treated with gemfibrozil at 10 times the human dose.

PRECAUTIONS

1. **Initial Therapy** – Laboratory studies should be done to ascertain that the lipid levels are consistently abnormal. Before instituting Lopid therapy, every attempt should be made to control serum lipids with appropriate diet, exercise, weight loss in obese patients, and control of any medical problems such as diabetes mellitus and hypothyroidism that are contributing to the lipid abnormalities.

2. **Continued Therapy** – Periodic determination of serum lipids should be obtained, and the drug withdrawn if lipid response is inadequate after 3 months of therapy.

3. **Drug Interactions** – (A) **HMG-CoA reductase inhibitors:** Rhabdomyolysis has occurred with combined gemfibrozil and lovastatin therapy. It may be seen as early as 3 weeks after initiation of combined therapy or after several months. In most subjects who have had an unsatisfactory lipid response to either drug alone, the possible benefit of combined therapy with lovastatin (or other HMG-CoA reductase inhibitors) and gemfibrozil does not outweigh the risks of severe myopathy, rhabdomyolysis, and acute renal failure. There is no assurance that periodic monitoring of creatine kinase will prevent the occurrence of severe myopathy and kidney damage.

(B) **Anticoagulants:** CAUTION SHOULD BE EXERCISED WHEN ANTICOAGULANTS ARE GIVEN IN CONJUNCTION WITH LOPID. THE DOSAGE OF THE ANTICOAGULANT SHOULD BE REDUCED TO MAINTAIN THE PROTHROMBIN TIME AT THE DESIRED LEVEL TO PREVENT BLEEDING COMPLICATIONS. FREQUENT PROTHROMBIN DETERMINATIONS ARE ADVISABLE UNTIL IT HAS BEEN DEFINITELY DETERMINED THAT THE PROTHROMBIN LEVEL HAS STABILIZED.

4. **Carcinogenesis, Mutagenesis, Impairment of Fertility** – Long-term studies have been conducted in rats at 0.2 and 2 times the human dose (based on surface area, mg/meter^2). The incidence of benign liver nodules and liver carcinomas was significantly increased in high dose male rats. The incidence of liver carcinomas increased also in low dose males, but this increase was not statistically significant ($p = 0.1$). Male rats had a dose-related and statistically significant increase of benign Leydig cell tumors. The higher dose female rats had a significant increase in the combined incidence of benign, and malignant liver neoplasms.

Long-term studies have been conducted in mice at 0.1 and 1 times the human dose (based on surface area). There were no statistically significant differences from controls in the incidence of liver tumors, but the doses tested were lower than those shown to be carcinogenic with other fibrates.

Electron microscopy studies have demonstrated a florid hepatic peroxisome proliferation following Lopid administration to the male rat. An adequate study to test for peroxisome proliferation has not been done in humans but changes in peroxisome morphology have been observed. Peroxisome proliferation has been shown to occur in humans with either of two other drugs of the fibrate class when liver biopsies were compared before and after treatment in the same individual.

Administration of approximately 0.6 and 2 times the human dose (based on surface area) to male rats for 10 weeks resulted in a dose-related decrease of fertility. Subsequent studies demonstrated that this effect was reversed after a drug-free period of about eight weeks, and it was not transmitted to the offspring.

5. **Pregnancy Category C** – Lopid has been shown to produce adverse effects in rats and rabbits at doses between 0.5 and 3 times the human dose (based on surface area) but no developmental toxicity or teratogenicity among offspring of either species. There are no adequate and well-controlled studies in pregnant women. Lopid should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Administration of Lopid to female rats at 0.6 and 2 times the human dose (based on surface area) before and throughout gestation caused a dose-related decrease in conception rate and, at the high dose, an increase in stillborns and a slight reduction in pup weight during lactation. There were also dose-related increased skeletal variations. Anophthalmia occurred, but rarely.

Administration of 0.6 and 2 times the human dose (based on surface area) of Lopid to female rats from gestation day 15 through weaning caused dose-related decreases in birth weight and suppressions of pup growth during lactation.

Administration of 1 and 3 times the human dose (based on surface area) of Lopid to female rabbits during organogenesis caused a dose-related decrease in litter size and at the high dose, an increased incidence of parietal bone variations.

6. **Nursing Mothers** – It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for tumorigenicity shown for Lopid in animal studies, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

7. **Hematologic Changes** – Mild hemoglobin, hematocrit and white blood cell decreases have been observed in occasional patients following initiation of Lopid therapy. However, these levels stabilize during long-term administration. Rarely, severe anemia, leukopenia, thrombocytopenia, and bone marrow hypoplasia have been reported. Therefore, periodic blood counts are recommended during the first 12 months of Lopid administration.

8. **Liver Function** – Abnormal liver function tests have been observed occasionally during Lopid administration, including elevations of AST (SGOT), ALT (SGPT), LDH, bilirubin, and alkaline phosphatase. These are usually reversible when Lopid is discontinued. Therefore periodic liver function studies are recommended and Lopid therapy should be terminated if abnormalities persist.

9. **Kidney Function** – There have been reports of worsening renal insufficiency upon the addition of Lopid therapy in individuals with baseline plasma creatinine > 2.0 mg/dL. In such patients, the use of alternative therapy should be considered against the risks and benefits of a lower dose of Lopid.

10. **Use in Children** – Safety and efficacy in children and adolescents have not been established.

ADVERSE REACTIONS

In the double-blind controlled phase of the primary prevention component of the Helsinki Heart Study, 2046 patients received Lopid for up to 5 years. In that study, the following adverse reactions were statistically more frequent in subjects in the Lopid group:

	LOPID (N=2046)	PLACEBO (N=2035)
	Frequency in percent of subjects	
Gastrointestinal reactions	34.2	23.8
Dyspepsia	19.6	11.9
Abdominal pain	9.8	5.6
Acute appendicitis (histologically confirmed in most cases where data were available)	1.2	0.6
Atrial fibrillation	0.7	0.1
Adverse events reported by more than 1% of subjects, but without a significant difference between groups:		
Diarrhea	7.2	6.5
Fatigue	3.8	3.5
Nausea/Vomiting	2.5	2.1
Eczema	1.9	1.2
Rash	1.7	1.3
Vertigo	1.5	1.3
Constipation	1.4	1.3
Headache	1.2	1.1

Gallbladder surgery was performed in 0.9% of Lopid and 0.5% of placebo subjects in the primary prevention component, a 64% excess, which is not statistically different from the excess of gallbladder surgery observed in the clofibrate compared to the placebo group of the WHO study. Gallbladder surgery was also performed more frequently in the Lopid group compared to placebo (1.9% vs. 0.3%, $p = 0.07$) in the secondary prevention component. A statistically significant increase in appendectomy in the gemfibrozil group was seen also in the secondary prevention component (6 on gemfibrozil vs. 0 on placebo, $p = 0.014$).

Nervous system and special senses adverse reactions were more common in the Lopid group. These included hypesthesia, paresthesias, and taste perversion. Other adverse reactions that were more common among Lopid treatment group subjects but where a causal relationship was not established include cataracts, peripheral vascular disease, and intracerebral hemorrhage.

From other studies it seems probable that Lopid is causally related to the occurrence of MUSCULOSKELETAL SYMPTOM (see WARNINGS), and to ABNORMAL LIVER FUNCTION TESTS and HEMATOLOGIC CHANGES (see PRECAUTIONS).

Reports of viral and bacterial infections (common cold, cough, urinary tract infections) were more common in gemfibrozil treated patients in other controlled clinical trials of 805 patients. Additional adverse reactions that have been reported for gemfibrozil are listed below by system. These are categorized according to whether a causal relationship to treatment with Lopid is probable or not established:

CAUSAL RELATIONSHIP PROBABLE: *Gastrointestinal:* cholestatic jaundice; *Central Nervous System:* dizziness, somnolence, paresthesia, peripheral neuritis, decreased libido, depression, headache; *Eye:* blurred vision; *Genitourinary:* impotence; *Musculoskeletal:* myopathy, myasthenia, myalgia, painful extremities, arthralgia, synovitis, rhabdomyolysis (see WARNINGS and Drug Interactions under PRECAUTIONS); *Clinical Laboratory:* increased creatine phosphokinase, increased bilirubin, increased liver transaminases (AST [SGOT], ALT [SGPT]), increased alkaline phosphatase; *Hematopoietic:* anemia, leukopenia, bone marrow hypoplasia, eosinophilia; *Immunologic:* angioedema, laryngeal edema, urticaria; *Integumentary:* exfoliative dermatitis, rash, dermatitis, pruritus.

CAUSAL RELATIONSHIP NOT ESTABLISHED: *General:* weight loss; *Cardiac:* extrasystoles; *Gastrointestinal:* pancreatitis, hepatoma, colitis; *Central Nervous System:* confusion, convulsions, syncope; *Eye:* retinal edema; *Genitourinary:* decreased male fertility, renal dysfunction; *Clinical Laboratory:* positive antinuclear antibody; *Hematopoietic:* thrombocytopenia; *Immunologic:* anaphylaxis, Lupus-like syndrome, vasculitis; *Integumentary:* alopecia.

DOSAGE AND ADMINISTRATION

The recommended dose for adults is 1200 mg administered in two divided doses 30 minutes before the morning and evening meal.

OVERDOSAGE

While there has been no reported case of overdosage, symptomatic supportive measures should be taken should it occur.

HOW SUPPLIED

Lopid (Tablet 737), white, elliptical, film-coated, scored tablets, each containing 600 mg gemfibrozil, are available as follows:

N 0071-0737-20 Bottles of 60
N 0071-0737-30 Bottles of 500
N 0071-0737-40 Unit dose packages of 100 (10 strips of 10 tablets each)
Parcode® No. 737

Storage: Store below 30° C (86° F).

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Caution – Federal law prohibits dispensing without prescription.

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Revised April 1992

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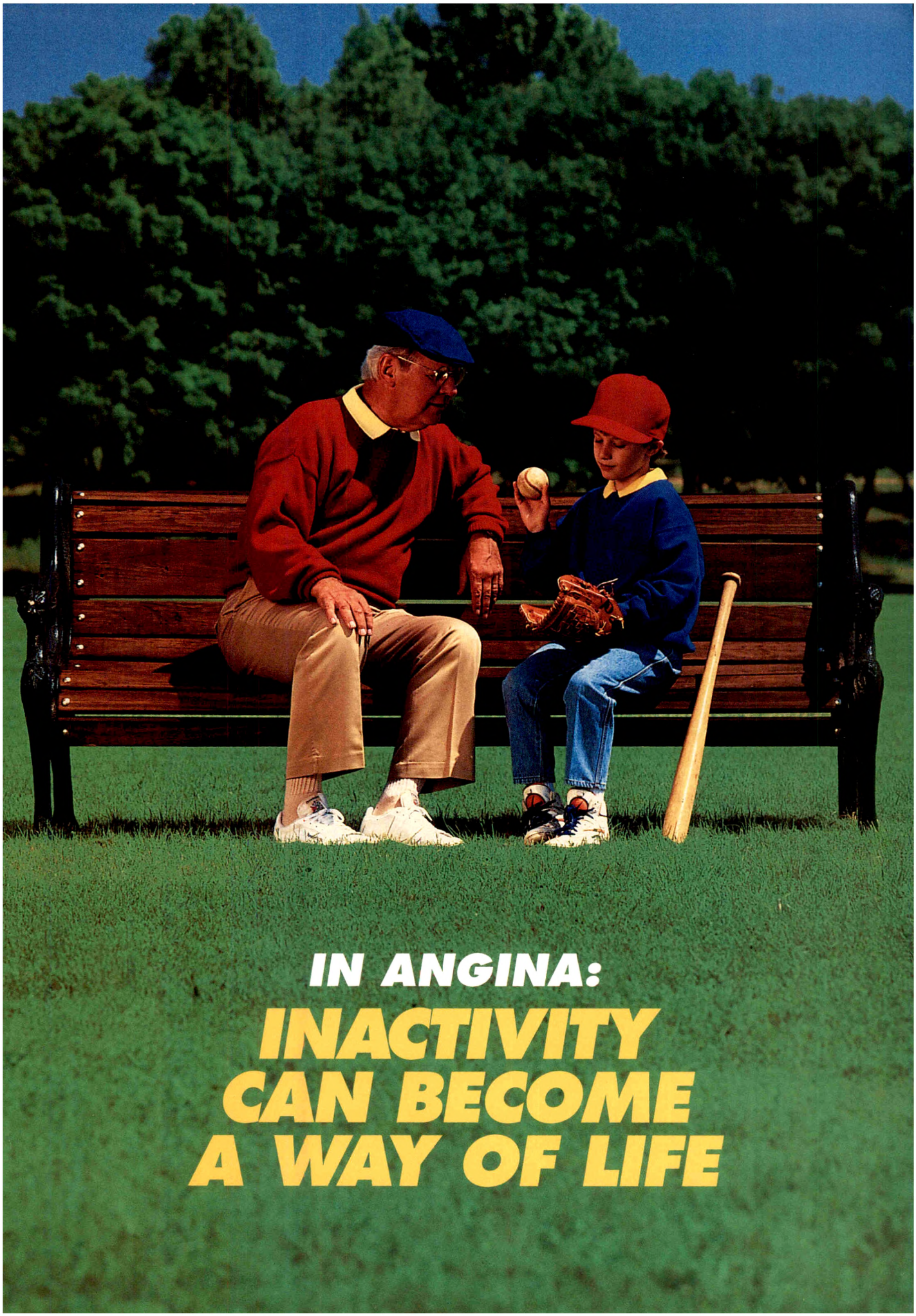
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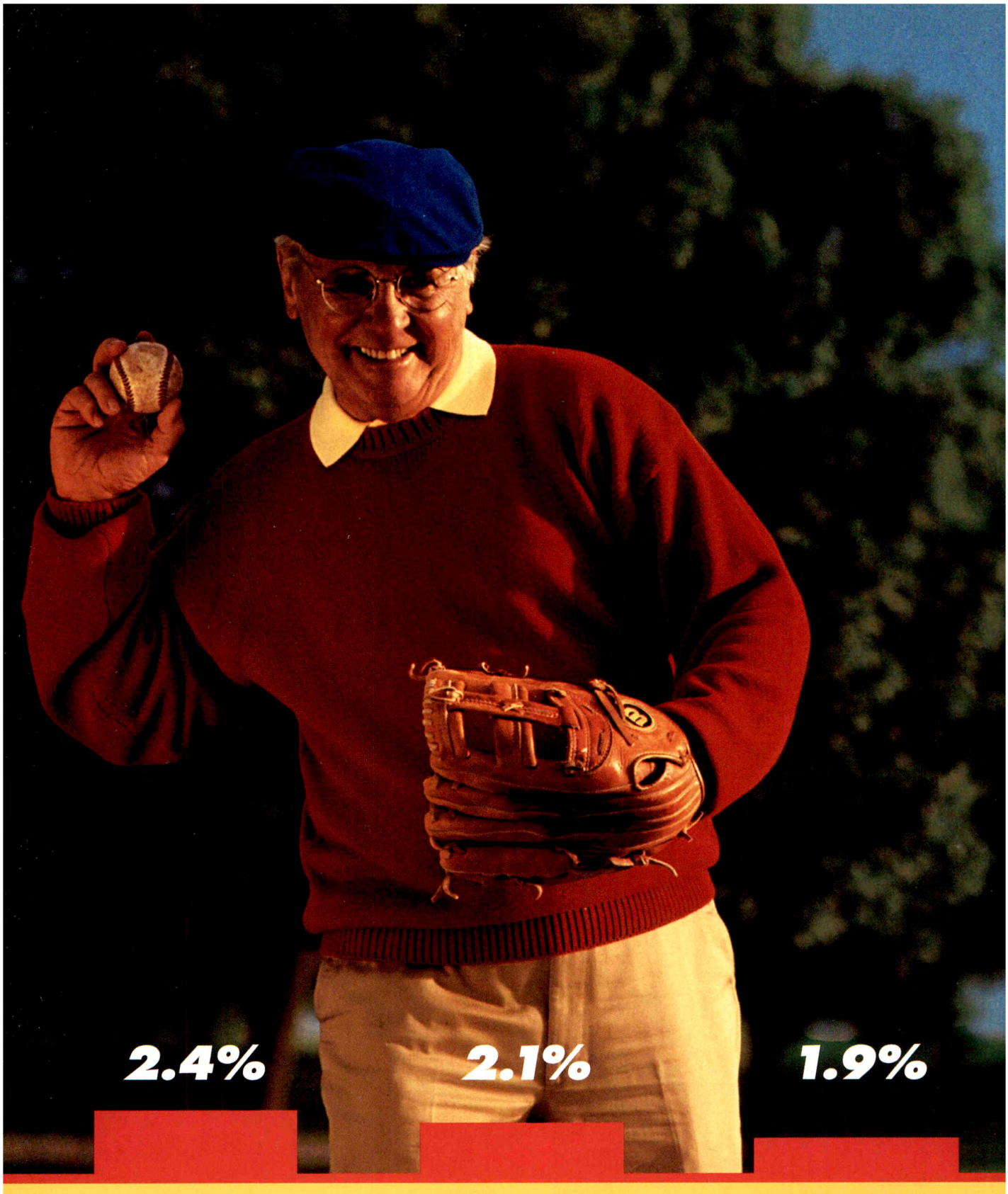
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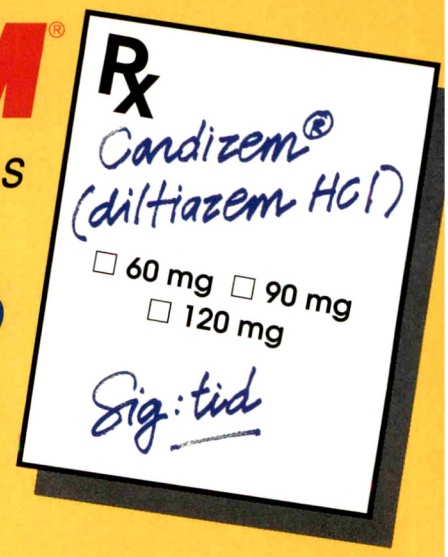

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BRIEF SUMMARY
CARDIZEM®
(diltiazem hydrochloride) Tablets

CONTRAINDICATIONS

CARDIZEM is contraindicated in (1) patients with sick sinus syndrome except in the presence of a functioning ventricular pacemaker, (2) patients with second- or third-degree AV block except in the presence of a functioning ventricular pacemaker, (3) patients with hypotension (less than 90 mm Hg systolic), (4) patients who have demonstrated hypersensitivity to the drug, and (5) patients with acute myocardial infarction and pulmonary congestion documented by x-ray on admission.

WARNINGS

1. **Cardiac Conduction.** CARDIZEM prolongs AV node refractory periods without significantly prolonging sinus node recovery time, except in patients with sick sinus syndrome. This effect may rarely result in abnormally slow heart rates (particularly in patients with sick sinus syndrome) or second- or third-degree AV block (six of 1,243 patients for 0.48%). Concomitant use of diltiazem with beta-blockers or digitalis may result in additive effects on cardiac conduction. A patient with Prinzmetal's angina developed periods of asystole (2 to 5 seconds) after a single dose of 60 mg of diltiazem.
2. **Congestive Heart Failure.** Although diltiazem has a negative inotropic effect in isolated animal tissue preparations, hemodynamic studies in humans with normal ventricular function have not shown a reduction in cardiac index nor consistent negative effects on contractility (dp/dt). Experience with the use of CARDIZEM alone or in combination with beta-blockers in patients with impaired ventricular function is very limited. Caution should be exercised when using the drug in such patients.
3. **Hypotension.** Decreases in blood pressure associated with CARDIZEM therapy may occasionally result in symptomatic hypotension.
4. **Acute Hepatic Injury.** In rare instances, significant elevations in enzymes such as alkaline phosphatase, LDH, SGOT, SGPT, and other phenomena consistent with acute hepatic injury have been noted. These reactions have been reversible upon discontinuation of drug therapy. The relationship to CARDIZEM is uncertain in most cases, but probable in some. (See PRECAUTIONS.)

PRECAUTIONS

General. CARDIZEM (diltiazem hydrochloride) is extensively metabolized by the liver and excreted by the kidneys and in bile. As with any drug given over prolonged periods, laboratory parameters should be monitored at regular intervals. The drug should be used with caution in patients with impaired renal or hepatic function. In subacute and chronic dog and rat studies designed to produce toxicity, high doses of diltiazem were associated with hepatic damage. In special subacute hepatic studies, oral doses of 125 mg/kg and higher in rats were associated with histological changes in the liver which were reversible when the drug was discontinued. In dogs, doses of 20 mg/kg were also associated with hepatic changes; however, these changes were reversible with continued dosing.

Dermatological events (see ADVERSE REACTIONS section) may be transient and may disappear despite continued use of CARDIZEM. However, skin eruptions progressing to erythema multiforme and/or exfoliative dermatitis have also been infrequently reported. Should a dermatologic reaction persist, the drug should be discontinued.

Drug Interaction. Due to the potential for additive effects, caution and careful titration are warranted in patients receiving CARDIZEM concomitantly with any agents known to affect cardiac contractility and/or conduction. (See WARNINGS.)

Pharmacologic studies indicate that there may be additive effects in prolonging AV conduction when using beta-blockers or digitalis concomitantly with CARDIZEM. (See WARNINGS.)

As with all drugs, care should be exercised when treating patients with multiple medications. CARDIZEM undergoes biotransformation by cytochrome P-450 mixed function oxidase. Coadministration of CARDIZEM with other agents which follow the same route of biotransformation may result in the competitive inhibition of metabolism. Dosages of similarly metabolized drugs, particularly those of low therapeutic ratio or in patients with renal and/or hepatic impairment, may require adjustment when starting or stopping concomitantly administered CARDIZEM to maintain optimum therapeutic blood levels.

Beta-blockers: Controlled and uncontrolled domestic studies suggest that concomitant use of CARDIZEM and beta-blockers or digitalis is usually well tolerated. Available data are not sufficient, however, to predict the effects of concomitant treatment, particularly in patients with left ventricular dysfunction or cardiac conduction abnormalities.

Administration of CARDIZEM (diltiazem hydrochloride) concomitantly with propranolol in five normal volunteers resulted in increased propranolol levels in all subjects and bioavailability of propranolol was increased approximately 50%. If combination therapy is initiated or withdrawn in conjunction with propranolol, an adjustment in the propranolol dose may be warranted. (See WARNINGS.)

Cimetidine: A study in six healthy volunteers has shown a significant increase in peak diltiazem plasma levels (58%) and area-under-the-curve (53%) after a 1-week course of cimetidine at 1,200 mg per day and diltiazem 60 mg per day. Ranitidine produced smaller, nonsignificant increases. The effect may be mediated by cimetidine's known inhibition of hepatic cytochrome P-450, the enzyme system probably responsible for the first-pass metabolism of diltiazem. Patients currently receiving diltiazem therapy should be carefully monitored for a change in pharmacological effect when initiating and discontinuing therapy with cimetidine. An adjustment in the diltiazem dose may be warranted.

Digitalis: Administration of CARDIZEM with digoxin in 24 healthy male subjects increased plasma digoxin concentrations approximately 20%. Another investigator found no increase in digoxin levels in 12 patients with coronary artery disease. Since there have been conflicting results regarding the effect of digoxin levels, it is recommended that digoxin levels be monitored when initiating, adjusting, and discontinuing CARDIZEM therapy to avoid possible over- or under-digitalization. (See WARNINGS.)

Anesthetics: The depression of cardiac contractility, conductivity, and automaticity as well as the vascular dilation associated with anesthetics may be potentiated by calcium channel blockers. When used concomitantly, anesthetics and calcium blockers should be titrated carefully.

Carcinogenesis, Mutagenesis, Impairment of Fertility. A 24-month study in rats and a 21-month study in mice showed no evidence of carcinogenicity. There was also no mutagenic response in in vitro bacterial tests. No intrinsic effect on fertility was observed in rats.

Pregnancy. Category C. Reproduction studies have been conducted in mice, rats, and rabbits. Administration of doses ranging from five to ten times greater (on a mg/kg basis) than the daily recommended therapeutic dose has resulted in embryo and fetal lethality. These doses, in some studies, have been reported to cause skeletal abnormalities. In the perinatal/postnatal studies, there was some reduction in early individual pup weights and survival rates. There was an increased incidence of stillbirths at doses of 20 times the human dose or greater.

There are no well-controlled studies in pregnant women; therefore, use CARDIZEM in pregnant women only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers. Diltiazem is excreted in human milk. One report suggests that concentrations in breast milk may approximate serum levels. If use of CARDIZEM is deemed essential, an alternative method of infant feeding should be instituted.

Pediatric Use. Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Serious adverse reactions have been rare in studies carried out to date, but it should be recognized that patients with impaired ventricular function and cardiac conduction abnormalities have usually been excluded.

In domestic placebo-controlled angina trials, the incidence of adverse reactions reported during CARDIZEM therapy was not greater than that reported during placebo therapy.

The following represent occurrences observed in clinical studies of angina patients. In many cases, the relationship to CARDIZEM has not been established. The most common occurrences from these studies, as well as their frequency of presentation, are: edema (2.4%), headache (2.1%), nausea (1.9%), dizziness (1.5%), rash (1.3%), asthenia (1.2%). In addition, the following events were reported infrequently (less than 1%):

Cardiovascular:	Angina, arrhythmia, AV block (first degree), AV block (second or third degree—see conduction warning), bradycardia, bundle branch block, congestive heart failure, ECG abnormality, flushing, hypotension, palpitations, syncope, tachycardia, ventricular extrasystoles.
Nervous System:	Abnormal dreams, amnesia, depression, gait abnormality, hallucinations, insomnia, nervousness, paresthesia, personality change, somnolence, tremor.
Gastrointestinal:	Anorexia, constipation, diarrhea, dysgeusia, dyspepsia, mild elevations of alkaline phosphatase, SGOT, SGPT, and LDH (see hepatic warnings), thirst, vomiting, weight increase.
Dermatological:	Petechiae, photosensitivity, pruritus, urticaria.
Other:	Amblyopia, CPK elevation, dry mouth, dyspnea, epistaxis, eye irritation, hyperglycemia, hyperuricemia, impotence, muscle cramps, nasal congestion, nocturia, osteoarticular pain, polyuria, sexual difficulties, tinnitus.

The following postmarketing events have been reported infrequently in patients receiving CARDIZEM: alopecia, erythema multiforme, extrapyramidal symptoms, gingival hyperplasia, hemolytic anemia, increased bleeding time, leukopenia, purpura, retinopathy, and thrombocytopenia. There have been observed cases of a generalized rash, characterized as leukocytoclastic vasculitis. In addition, events such as myocardial infarction have been observed which are not readily distinguishable from the natural history of the disease in these patients. A definitive cause and effect relationship between these events and CARDIZEM therapy cannot yet be established. Exfoliative dermatitis (proven by rechallenge) has also been reported.

HOW SUPPLIED

CARDIZEM® (diltiazem hydrochloride) is available in bottles of 90 (60 mg, 90 mg, 120 mg tablets), bottles of 100 (30 mg, 60 mg, 90 mg, 120 mg tablets), bottles of 500 (30 mg, 60 mg tablets), and UDIP® packages of 100.

Issued 1/91(a)

MARION MERRELL DOW INC.
PRESCRIPTION PRODUCTS DIVISION
KANSAS CITY, MO 64114

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The American Journal of Cardiology®

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The American Journal of Cardiology®

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CORONARY ARTERY DISEASE

703

Identification of Viable Myocardium by Dipyridamole-Induced Improvement in Regional Left Ventricular Function Assessed by Echocardiography in Myocardial Infarction and Comparison with Thallium Scintigraphy at Rest

Eugenio Picano, Paolo Marzullo, Guido Gigli, Barbara Reisenhofer, Oberdan Parodi, Alessandro Distante, and Antonio L'Abbate

The aim of this study was to assess whether the increase in regional left ventricular function early during dipyridamole infusion in basally asynergic segments could identify viable myocardium recognized by injected, delayed (>14 hours from tracer injection) thallium at rest and (in a subset of patients) by late functional recovery at a follow-up echocardiogram at rest. Twenty-two patients with angiographically documented coronary artery disease and regional dysfunction in resting conditions (average left ventricular ejection fraction 43 ± 8%) were studied by echocardiography. All patients underwent a dipyridamole-echocardiographic test (up to 0.84 mg/kg over 10 minutes) and a delayed planar thallium study. A segment was considered viable when there was a regional activity >55% of peak thallium and when a resting dyssynergy (echo score ≥2) showed an improvement of ≥1 grade by dipyridamole. In all, 80 basally asynergic segments were scored. The 23 segments viable by dipyridamole had higher thallium score than did the 57 necrotic by dipyridamole (73 ± 9 vs 42 ± 9; $p < 0.01$). In a subset of 15 patients, a follow-up echocardiogram at rest was obtained at 3.4 ± 2.7 months after the initial study. A significant functional recovery (improvement of ≥1 grade) was found in 15 of 19 segments with and only 5 of 39 without dipyridamole-induced improvement (79 vs 13%; $p < 0.01$). These observations suggest that dipyridamole-induced recovery in contractile function of basally asynergic segments (possibly linked to the inotropic effect of increased flow) identifies areas with myocardial viability.

711

Doppler Echocardiographic Patterns of Left Ventricular Filling in Patients Early After Acute Myocardial Infarction

Adrian Chenzbraun, Andre Keren, and Shlomo Stern

Diastolic function was studied by Doppler parameters of left ventricular filling in 15 control subjects and 38 patients 11 ± 7 days after acute myocardial infarction. Ratios between peak flow velocities during early

Continued on page A17

THEY WERE CAREFREE...

They were raised in a simpler time, before sugar-free and fat-free. Now hypertension, often with elevated cholesterol and blood sugar, enters the picture...







NOW THEY'RE CONCERNED...

Today's hypertensives with new concerns...

THE CARDURA



*Adapted from the interim (12 months) results of the Treatment of Mild Hypertension Study, a randomized, double-blind, placebo-controlled trial of a nutritional-hygienic regimen along with various dr therapies. All drugs (except acebutolol) were given initially in low doses. If the patient showed a diastolic blood pressure more than 95 mm Hg on three successive follow-up visits, the dosage was doubled. If blood pressure remained elevated, a second drug (chlorthalidone, except for chlorthalidone group, which was given enalapril) was added. Mean diastolic blood pressure was lowered in various drug groups with median dosages, as follows: doxazosin (2 mg/day), 12.0 mm Hg; enalapril (5 mg/day), 12.2 mm Hg; chlorthalidone (15 mg/day), 13.1 mm Hg; and acebutolol (400 mg/day) 13.7 mm Hg (n=847; $P<0.01$ vs placebo).

†n=128; $P<0.01$ vs placebo. In a pooled analysis of placebo-controlled studies with about 300 predominantly normocholesterolemic patients per treatment group, CARDURA produced a small decrea in total cholesterol (-2.7%) and LDL cholesterol (-4.3%) and a small increase in the HDL/total cholesterol ratio (+4.3%).

‡Adapted from Lehtonen et al[2] (n=77; after 26 weeks: $P<0.001$ compared with week 0 for blood pressure and insulin, $P<0.05$ compared with week 0 for glucose).

GENERATION



Choose CARDURA: first-line therapy for a new generation of hypertensives.

Choose CARDURA for blood pressure control that doesn't jeopardize blood lipids.

In the Treatment of Mild Hypertension Study, CARDURA lowered diastolic blood pressure (mean 12.0 mm Hg) as effectively as enalapril, chlorthalidone, and acebutolol[1*]

CARDURA lowered blood pressure with a small increase in the HDL/total cholesterol ratio (+2.4%)* in the same study.[1†] The clinical significance of these changes is uncertain. Cholesterol is just one parameter to consider when selecting the best individualized therapy for a given patient

Choose CARDURA for blood pressure control that doesn't compromise blood sugar.

CARDURA controlled diastolic blood pressure without an adverse effect on glucose tolerance or insulin control[2‡]

CARDURA is well tolerated. In placebo-controlled studies, only three common side effects were reported significantly more often than placebo: dizziness, somnolence, and fatigue.[§]

Only 2% of patients discontinued therapy due to adverse effects—the same as with placebo

§ These were generally mild and transient. Syncope has been reported, but rarely (<1%).

ONCE-A-DAY

CARDURA®

(doxazosin mesylate) Scored Tablets 1 mg, 2 mg, 4 mg, 8 mg

HYPERTENSION CONTROL FOR A NEW GENERATION.

Please see brief summary on last page.

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ONCE-A-DAY

CARDURA®

(doxazosin mesylate) Scored Tablets 1 mg, 2 mg, 4 mg, 8 mg

CARDURA® (doxazosin mesylate) Tablets
Brief Summary of Prescribing Information

INDICATIONS AND USAGE

CARDURA (doxazosin mesylate) is indicated for the treatment of hypertension. CARDURA may be used alone or in combination with diuretics or beta-adrenergic blocking agents. There is limited experience with CARDURA in combination with angiotensin converting enzyme inhibitors or calcium channel blockers.

CONTRAINDICATIONS

CARDURA is contraindicated in patients with a known sensitivity to quinazolines (e.g. prazosin, terazosin).

WARNINGS

Syncope and "First-dose" Effect:

Doxazosin, like other alpha-adrenergic blocking agents, can cause marked hypotension, especially in the upright position, with syncope and other postural symptoms such as dizziness. Marked orthostatic effects are most common with the first dose but can also occur when there is a dosage increase, or if therapy is interrupted for more than a few days. To decrease the likelihood of excessive hypotension and syncope, it is essential that treatment be initiated with the 1 mg dose. The 2, 4, and 8 mg tablets are not for initial therapy. Dosage should then be adjusted slowly (see DOSAGE AND ADMINISTRATION section) with increases in dose every two weeks. Additional antihypertensive agents should be added with caution.

Patients being titrated with doxazosin should be cautioned to avoid situations where injury could result should syncope occur.

In an early investigational study of the safety and tolerance of increasing daily doses of doxazosin in normotensives beginning at 1 mg/day, only 2 of 6 subjects could tolerate more than 2 mg/day without experiencing symptomatic postural hypotension. In another study of 24 healthy normotensive male subjects receiving initial doses of 2 mg/day of doxazosin, seven (29%) of the subjects experienced symptomatic postural hypotension between 0.5 and 6 hours after the first dose necessitating termination of the study. In this study 2 of the normotensive subjects experienced syncope. Subsequent trials in hypertensive patients always began doxazosin dosing at 1 mg/day resulting in a 4% incidence of postural side effects at 1 mg/day with no cases of syncope.

In multiple dose clinical trials involving over 1500 patients with dose titration every one to two weeks, syncope was reported in 0.7% of patients. None of these events occurred at the starting dose of 1 mg and 1.2% (8/664) occurred at 16 mg/day.

If syncope occurs, the patient should be placed in a recumbent position and treated supportively as necessary.

PRECAUTIONS

General

1. Orthostatic Hypotension:

While syncope is the most severe orthostatic effect of CARDURA, other symptoms of lowered blood pressure, such as dizziness, lightheadedness, or vertigo, can occur, especially at initiation of therapy or at the time of dose increases. These were common in clinical trials, occurring in up to 23% of all patients treated and causing discontinuation of therapy in about 2%.

In placebo controlled titration trials orthostatic effects were minimized by beginning therapy at 1 mg per day and titrating every two weeks to 2, 4, or 8 mg per day. There was an increased frequency of orthostatic effects in patients given 8 mg or more, 10%, compared to 5% at 1-4 mg and 3% in the placebo group.

Patients in occupations in which orthostatic hypotension could be dangerous should be treated with particular caution.

If hypotension occurs, the patient should be placed in the supine position and, if this measure is inadequate, volume expansion with intravenous fluids or vasopressor therapy may be used. A transient hypotensive response is not a contraindication to further doses of CARDURA.

2. Impaired liver function:

CARDURA should be administered with caution to patients with evidence of impaired hepatic function or to patients receiving drugs known to influence hepatic metabolism (see CLINICAL PHARMACOLOGY). There is no controlled clinical experience with CARDURA in patients with these conditions.

3. Leukopenia/Neutropenia:

Analysis of hematologic data from patients receiving CARDURA in controlled clinical trials showed that the mean WBC (N=474) and mean neutrophil counts (N=419) were decreased by 2.4% and 1.0% respectively, compared to placebo, a phenomenon seen with other alpha blocking drugs. A search through a data base of 2400 patients revealed 4 in which drug-related neutropenia could not be ruled out. Two had a single low value on the last day of treatment. Two had stable, non-progressive neutrophil counts in the 1000/mm³ range over periods of 20 and 40 weeks. In cases where follow-up was available the WBCs and neutrophil counts returned to normal after discontinuation of CARDURA. No patients became symptomatic as a result of the low WBC or neutrophil counts.

Information for Patients:

Patients should be made aware of the possibility of syncopal and orthostatic symptoms, especially at the initiation of therapy, and urged to avoid driving or hazardous tasks for 24 hours after the first dose, after a dosage increase, and after interruption of therapy when treatment is resumed. They should be cautioned to avoid situations where injury could result should syncope occur during initiation of doxazosin therapy. They should also be advised of the need to sit or lie down when symptoms of lowered blood pressure occur, although these symptoms are not always orthostatic, and to be careful when rising from a sitting or lying position. If dizziness, lightheadedness, or palpitations are bothersome they should be reported to the physician, so that dose adjustment can be considered. Patients should also be told that drowsiness or somnolence can occur with doxazosin, requiring caution in people who must drive or operate heavy machinery.

Drug Interactions:

Most (98%) of plasma doxazosin is protein bound. *In vitro* data in human plasma indicate that CARDURA has no effect on protein binding of digoxin, warfarin, phenytoin or indomethacin. There is no information on the effect of other highly plasma protein bound drugs on doxazosin binding. CARDURA has been administered without any evidence of an adverse drug interaction to patients receiving thiazide diuretics, beta blocking agents, and nonsteroidal anti-inflammatory drugs.

Drug/Laboratory test interactions:

None known.

Cardiac Toxicity in Animals:

An increased incidence of myocardial necrosis or fibrosis was displayed by Sprague-Dawley rats after 6 months of dietary administration at concentrations calculated to provide 80 mg doxazosin/kg/day and after 12 months of dietary administration at concentrations calculated to provide 40 mg doxazosin/kg/day (150 times the maximum recommended human dose assuming a patient weight of 60 kg). Myocardial fibrosis was observed in both rats and mice treated in the same manner with 40 mg doxazosin/kg/day for 18 months. No cardiotoxicity was observed at lower doses (up to 10 or 20 mg/kg/day, depending on the study) in either species. These lesions were not observed after 12 months of oral dosing in dogs and Wistar rats at maximum doses of 20 mg/kg/day and 100 mg/kg/day, respectively. There is no evidence that similar lesions occur in humans.

Carcinogenesis, Mutagenesis and Impairment of Fertility:

Chronic dietary administration (up to 24 months) of doxazosin mesylate at maximally tolerated concentrations (highest dose 40 mg/kg: about 150 times the maximum recommended human dose of 16 mg/60 kg) revealed no evidence of carcinogenicity in rats. There was also no evidence of carcinogenicity in a similarly conducted study (up to 18 months of dietary administration) in mice. The mouse study, however, was compromised by the failure to use a maximally tolerated dose of doxazosin.

Mutagenicity studies revealed no drug- or metabolite-related effects at either chromosomal or subchromosomal levels.

Studies in rats showed reduced fertility in males treated with doxazosin at oral doses of 20 (but not 5 or 10) mg/kg/day, about 75 times the maximum recommended human dose. This effect was reversible within two weeks of drug withdrawal.

Pregnancy

Teratogenic Effects, Pregnancy Category B. Studies in rabbits and rats at daily oral doses of up to 40 and 20 mg/kg, respectively (150 and 75 times the maximum recommended daily dose of 16 mg, assuming a patient weight of 60 kg), have revealed no evidence of harm to the fetus. The rabbit study, however, was compromised by the failure to use a maximally tolerated dose of doxazosin. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, CARDURA should be used during pregnancy only if clearly needed.

Radioactivity was found to cross the placenta following oral administration of labelled doxazosin to pregnant rats.

Nonteratogenic Effects. In peri-postnatal studies in rats, postnatal development at maternal doses of 40 or 50 mg/kg/day of doxazosin was delayed as evidenced by slower body weight gain and a slightly later appearance of anatomical features and reflexes.



Nursing Mothers

Studies in lactating rats given a single oral dose of 1 mg/kg of [2-¹⁴C]-doxazosin indicate that doxazosin accumulates in rat breast milk with a maximum concentration about 20 times greater than the maternal plasma concentration. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when CARDURA is administered to a nursing mother.

Pediatric Use

Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

CARDURA has been administered to approximately 4000 patients, of whom 1679 were included in the clinical development program. In that program, minor adverse effects were frequent, but led to discontinuation of treatment in only 7% of patients. In placebo-controlled studies adverse effects occurred in 49% and 40% of patients in the doxazosin and placebo groups, respectively, and led to discontinuation in 2% of patients in each group. The major reasons for discontinuation were postural effects (2%), edema, malaise/fatigue, and some heart rate disturbance, each about 0.7%.

In controlled clinical trials directly comparing CARDURA to placebo there was no significant difference in the incidence of side effects, except for dizziness (including postural), weight gain, somnolence and fatigue / malaise. Postural effects and edema appeared to be dose related.

The prevalence rates presented below are based on combined data from placebo-controlled studies involving once daily administration of doxazosin at doses ranging from 1-16 mg. Table 1 summarizes those adverse experiences (possibly/probably related) reported for patients in these studies where the prevalence rate in the doxazosin group was at least 0.5% or where the reaction is of particular interest.

TABLE 1
ADVERSE REACTIONS DURING PLACEBO CONTROLLED STUDIES

		DOXAZOSIN (N=339)	PLACEBO (N=336)
CARDIOVASCULAR:	Dizziness	19%	9%
	Vertigo	2%	1%
	Postural Hypotension	0.3%	0%
	Edema	4%	3%
	Palpitation	2%	3%
	Arrhythmia	1%	0%
	Hypotension	1%	0%
	Tachycardia	0.3%	1%
	Peripheral Ischemia	0.3%	0%
SKIN APPENDAGES:	Rash	1%	1%
	Pruritus	1%	1%
MUSCULOSKELETAL:	Arthralgia/Arthritis	1%	0%
	Muscle Weakness	1%	0%
	Myalgia	1%	0%
CENTRAL & PERIPHERAL N.S.:	Headache	14%	16%
	Paresthesia	1%	1%
	Kinetic Disorders	1%	0%
	Ataxia	1%	0%
	Hypertonia	1%	0%
	Muscle Cramps	1%	0%
AUTONOMIC:	Mouth Dry	2%	2%
	Flushing	1%	0%
SPECIAL SENSES:	Vision Abnormal	2%	1%
	Conjunctivitis/Eye Pain	1%	1%
	Tinnitus	1%	0.3%
PSYCHIATRIC:	Somnolence	5%	1%
	Nervousness	2%	2%
	Depression	1%	1%
	Insomnia	1%	1%
	Sexual Dysfunction	2%	1%
GASTROINTESTINAL:	Nausea	3%	4%
	Diarrhea	2%	3%
	Constipation	1%	1%
	Dyspepsia	1%	1%
	Flatulence	1%	1%
	Abdominal Pain	0%	2%
	Vomiting	0%	1%
RESPIRATORY:	Rhinitis	3%	1%
	Dyspnea	1%	1%
	Epistaxis	1%	0%
URINARY:	Polyuria	2%	0%
	Urinary Incontinence	1%	0%
	Micturation Frequency	0%	2%
GENERAL:	Fatigue/Malaise	12%	6%
	Chest Pain	2%	2%
	Asthenia	1%	1%
	Face Edema	1%	0%
	Pain	2%	2%

Additional adverse reactions have been reported, but these are, in general not distinguishable from symptoms that might have occurred in the absence of exposure to doxazosin. The following adverse reactions occurred with a frequency of between 0.5% and 1%: syncope, hypoesthesia, increased sweating, agitation, increased weight. The following additional adverse reactions were reported by <0.5% of 3960 patients who received doxazosin in controlled or open, short- or long-term clinical studies, including international studies. *Cardiovascular System:* angina pectoris, myocardial infarction, cerebrovascular accident; *Autonomic Nervous System:* pallor; *Metabolic:* thirst, gout, hypokalemia; *Hematopoietic:* lymphadenopathy, purpura; *Reproductive System:* breast pain; *Skin Disorders:* alopecia, dry skin, eczema; *Central Nervous System:* paresis, tremor, twitching, confusion, migraine, impaired concentration; *Psychiatric:* paroniria, amnesia, emotional lability, abnormal thinking, depersonalization; *Special Senses:* parosmia, earache, taste perversion, photophobia, abnormal lacrimation; *Gastrointestinal System:* increased appetite, anorexia, fecal incontinence, gastroenteritis; *Respiratory System:* bronchospasm, sinusitis, coughing, pharyngitis; *Urinary System:* renal calculus; *General Body System:* flushes, back pain, infection, fever/rigors, decreased weight, influenza-like symptoms.

CARDURA has not been associated with any clinically significant changes in routine biochemical tests. No clinically relevant adverse effects were noted on serum potassium, serum glucose, uric acid, blood urea nitrogen, creatinine or liver function tests. CARDURA has been associated with decreases in white blood cell counts (See Precautions).

OVERDOSAGE

The oral LD_{50} of doxazosin is greater than 1000 mg/kg in mice and rats. The most likely manifestation of overdosage would be hypotension, for which the usual treatment would be intravenous infusion of fluid. As doxazosin is highly protein bound, dialysis would not be indicated.

DOSAGE AND ADMINISTRATION

DOSAGE MUST BE INDIVIDUALIZED. The initial dosage of CARDURA in hypertensive patients is 1 mg given once daily. This starting dose is intended to minimize the frequency of postural hypotension and first dose syncope associated with CARDURA. Postural effects are most likely to occur between 2 and 6 hours after a dose. Therefore blood pressure measurements should be taken during this time period after the first dose and with each increase in dose. Depending on the individual patient's standing blood pressure response (based on measurements taken at 2-6 hours postdose and 24 hours postdose), dosage may then be increased to 2 mg and thereafter if necessary to 4 mg, 8 mg and 16 mg to achieve desired reduction in blood pressure. **Increases in dose beyond 4 mg increase the likelihood of excessive postural effects including syncope, postural dizziness/vertigo, postural hypotension. At a titrated dose of 16 mg once daily the frequency of postural effects is about 12% compared to 3% for placebo.**

HOW SUPPLIED

CARDURA (doxazosin mesylate) is available as colored tablets for oral administration. Each tablet contains doxazosin mesylate equivalent to 1 mg (white), 2 mg (yellow), 4 mg (orange) or 8 mg (green) of the active constituent, doxazosin.

CARDURA® TABLETS are available as 1 mg (white), 2 mg (yellow), 4 mg (orange) and 8 mg (green) scored tablets.

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Recommended Storage: Store below 86°F(30°C).

CAUTION: Federal law prohibits dispensing without prescription.

65-4538-00-0 Issued Nov 1

References: 1. The Treatment of Mild Hypertension Research Group. The Treatment of Mild Hypertension Study: a randomized, placebo-controlled trial of a nutritional-hygienic regimen along with various drug monotherapies. *Arch Intern Med.* 1991;151:1413-1423. **2.** Lehtonen A, the Finnish Multicenter Study Group. Lowered levels of serum insulin, glucose, and cholesterol in hypertensive patients during treatment with doxazosin. *Curr Ther Res.* 1990;47:278-284.

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filling and atrial contraction (E/A) of <1, compatible with impaired relaxation, were found in 14 patients (37%), and abnormally high ratios (>2) were found in 5 patients (13%). Half of patients had a normal E/A ratio. Left ventricular end-diastolic pressure at catheterization was low or normal in patients with E/A ratios <1 and was usually >15 mm Hg in those with higher E/A ratios. Thus, an apparently normal E/A ratio in patients after myocardial infarction suggests more severe diastolic dysfunction.

715

Angiographic Findings in the Coronary Arteries After Thrombolysis in Acute Myocardial Infarction

Mervyn Gotsman, Shimon Rosenheck, Hisham Nassar, Sima Welber, Dan Sapoznikov, Morris Mosseri, Avraham Weiss, Chaim Lotan, and Yoseph Rozenman

The angiographic appearance of the coronary arteries was examined in 308 patients with acute myocardial infarction who received intravenous thrombolytic therapy. Patients had an average of 2.4 discrete arterial narrowings or obstructions. The narrowings were proximal and related to bifurcations. Four fifths of the culprit arteries were patent; 104 (34%) had a ruptured plaque, 22 (7%) had an ulcerated plaque, and in 190 (62%) the lesions were eccentric. Patients differed from a comparable, previously studied, control series of 302 patients with chronic stable angina pectoris who had more extensive disease and 5.7 narrowings/patient, also located proximally and at bifurcations, but more widely distributed in the coronary tree. Patients with acute myocardial infarction who are suitable for thrombolysis have a unique coronary angiographic picture.

724

Effect of Beta-Adrenoceptor Blockade on Dipyridamole-Induced Myocardial Asynergies in Coronary Artery Disease

Nicola Ferrara, Giancarlo Longobardi, Antonio Nicolino, Domenico Acanfora, Luigi Odierna, Giuseppe Furgi, Michele Rossi, Dario Leosco, and Franco Rengo

We prospectively studied 21 patients with angiographic evidence of significant coronary artery disease and positive dipyridamole echocardiographic test results at basal condition and after 7 days of placebo treatment, and with adequate echocardiography windows, to see whether β blockade modifies the response of the dipyridamole echocardiographic test. Thirteen of 21 patients had negative dipyridamole echocardiographic test results after propranolol treatment, whereas the remaining 8 continued to develop asynergies during the test despite β-adrenoceptor blockade. At the peak of dipyridamole infusion, heart rate and rate-pressure product were significantly lower in patients with negative than in patients with positive dipyridamole echocardiographic test results. Our data show that β blockade significantly reduces the development of transient dipyridamole-induced myocardial asynergies.

728

Analysis of the Signal-Averaged P-Wave Duration in Patients with Percutaneous Coronary Angioplasty–Induced Myocardial Ischemia

Michael M. Myrianthefs, Adrian H. Shandling, Ronald H. Startt-Selvester, Stephen B. Bernstein, Randy Crump, Linda M. Lorenz, Susan Switzenberg, and Myrvin H. Ellestad

The maximal signal-averaged P-wave duration and the maximal ST-segment shift was measured on ambulatory electrocardiographic recordings obtained in 47 patients undergoing elective angioplasty of major coronary arteries. For all patients, mean baseline P-wave duration in any lead was 125 ± 16 ms and 130 ± 15 ms during balloon inflation, $p < 0.005$. Significant increases in the P-wave duration were found to occur in groups both with ($n = 34$) and without ($n = 13$) ST-segment shift ≥1 mm (both $p < 0.05$). In the left anterior descending subgroup ($n = 23$), P-wave duration was 122.4 ± 17 ms at baseline and was 131.3 ± 16 ms during balloon inflation, $p < 0.005$. It is concluded that the duration of the signal-averaged surface P wave is prolonged during balloon inflation. This finding may prove useful in addition to conventional ST-T changes for detecting ischemia during ambulatory electrocardiographic monitoring and stress testing.

733

Relation of High-Density Lipoprotein Cholesterol and Triglycerides to Incidence of Atherosclerotic Coronary Artery Disease (the PROCAM Experience)

Gerd Assmann and Helmut Schulte

Atherosclerotic coronary artery disease (CAD) was assessed in 4,559 male participants (aged 40 to 64 years) from the Prospective Cardiovascular Münster (PROCAM) study. Over 6 years of follow-up, 186 study participants developed atherosclerotic CAD. Univariate analysis revealed a significant association between the incidence of atherosclerotic CAD and high-density lipoprotein (HDL) cholesterol ($p < 0.001$) and triglycerides ($p < 0.001$). The relation to HDL cholesterol remained after adjustment for other risk factors. By contrast, the relation between the incidence of atherosclerotic CAD and triglycerides disappeared if, in a multivariate analysis by means of a multiple logistic function, cholesterol or HDL cholesterol were taken into account. However, the data suggested that hypertriglyceridemia is a powerful additional coronary risk factor when excessive triglycerides coincide with a high ratio of plasma low-density lipoprotein cholesterol to HDL cholesterol (>5.0). Even though the prevalence of this subgroup was only 4.3%, it included one fourth of all atherosclerotic CAD events observed.

738

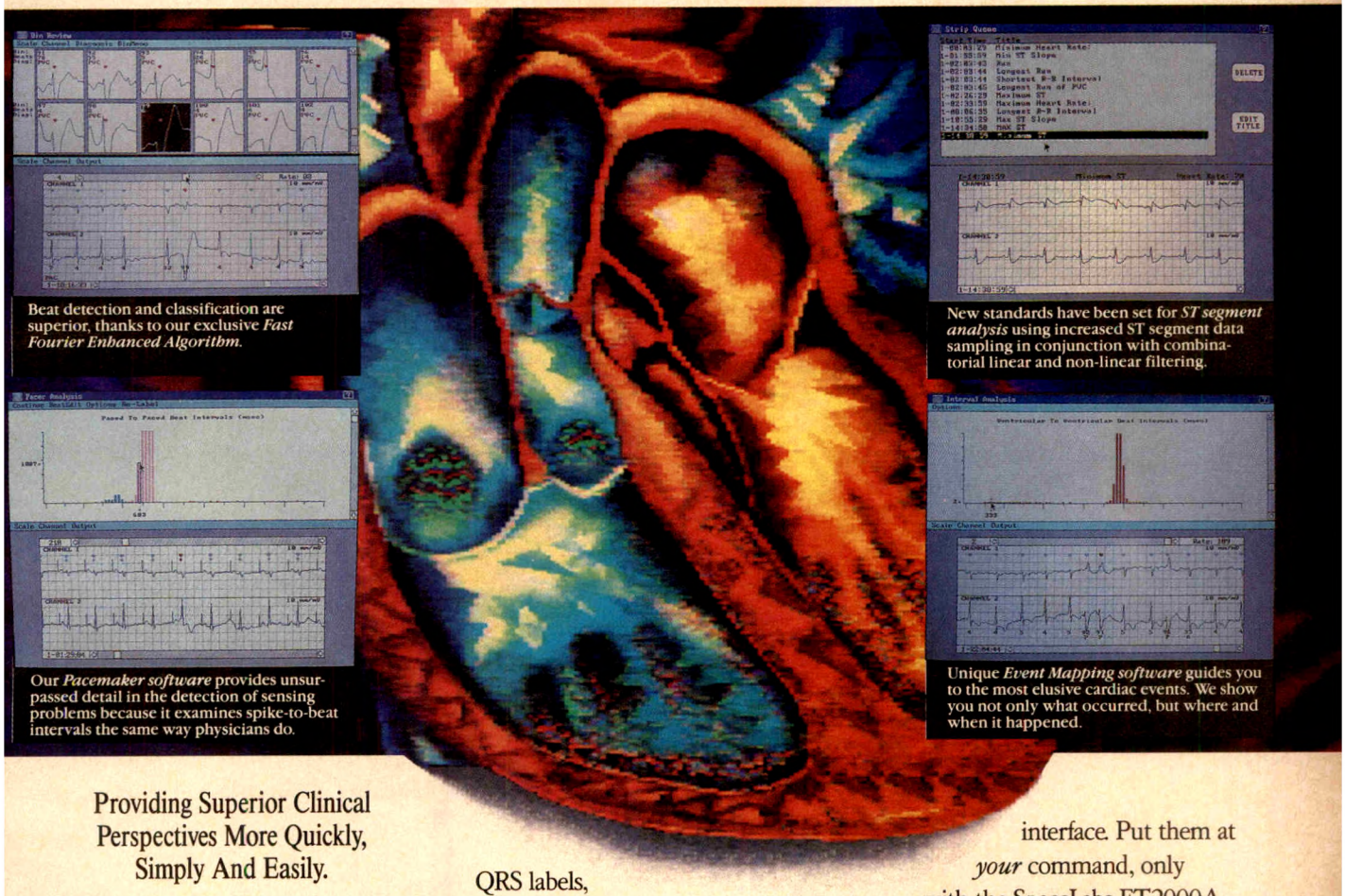
The Case for Unstable Angina Pectoris as a Primary End Point in Primary Prevention Studies

Edwin J. Whitney, Charles L. Shear, Geraldine Mantell, Eva Lydick, and Robert Wolf

The prevention of coronary artery disease (CAD) remains a high public health priority. Definitions used as primary end points in prior CAD

Continued on page A20

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primary prevention trials are reviewed. Secular trends in CAD mortality, the incidence of acute myocardial infarction, and hospital discharge rates indicate a shift toward the increasing role of angina as a major contributor to CAD morbidity. The currently available diagnostic technologies and high-risk pathology found with unstable angina warrant this condition to be seriously considered as a primary CAD end point in future primary prevention trials.

744

Asymptomatic Cardiac Ischemia Pilot Study (ACIP)

The ACIP Investigators

Limited data suggest that medical therapy or revascularization has the potential to alleviate myocardial ischemia. There are, however, no adequate data to evaluate long-term benefits and risks of the treatment to control asymptomatic cardiac ischemia. The National Heart, Lung, and Blood Institute has funded the Asymptomatic Cardiac Ischemia Pilot study to determine whether angina-directed, angina and ambulatory electrocardiographic-directed medical therapy or mechanical revascularization (angioplasty or surgery, or both) provides effective control of asymptomatic myocardial ischemia in patients with coronary artery disease. The results of the pilot study will influence the decision about whether a full-scale trial of amelioration of asymptomatic cardiac ischemia improves survival and reduces cardiovascular morbidity.

ARRHYTHMIAS AND CONDUCTION DISTURBANCES

748

Long-Term Prognostic Significance of Ambulatory Electrocardiographic Findings in Apparently Healthy Subjects ≥60 Years of Age

Jerome L. Fleg and Harold L. Kennedy

The long-term prognostic significance of frequent or complex ectopic beats and ST-segment changes on 24-hour ambulatory electrocardiogram was determined in 98 apparently healthy volunteers aged 60 to 85 years from the Baltimore Longitudinal Study of Aging. Over a mean follow-up period of 10 years, coronary events developed in 14 subjects. The incidence of coronary events did not differ significantly between subjects who developed the following arrhythmias and those who did not, respectively: ≥30 supraventricular ectopic beats in any hour, 18 vs 13%; ≥100 supraventricular ectopic beats in 24 hours, 20 vs 12%; paroxysmal atrial tachycardia, 15 vs 14%; ≥30 ventricular ectopic complexes (VECs) in any hour, 17 vs 14%; ≥100 VECs in 24 hours, 18 vs 14%; or repetitive VECs, 20 vs 13%. Coronary events occurred in 2 of the 5 subjects with flat or downsloping ST-segment depression ≥1.0 mm vs only 12 of 93 subjects (13%) without such ST-segment changes. When 11 additional patients with upsloping ST-segment depression were included, events occurred in 6 of 16 (38%) compared with 8 of 82 (10%) without any ST-segment changes, $p < 0.05$. Thus, neither supraventricular ectopic beats nor VEC patterns on the ambulatory electrocardiogram predict the development of future coronary

Continued on page A23

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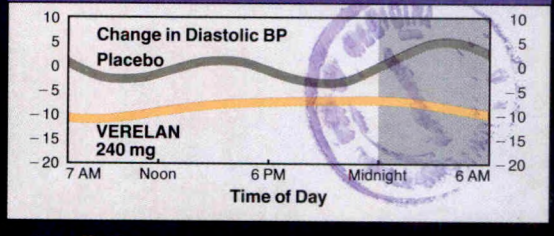
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P ROTECTS your hypertensive patients for 24 hours[1]

In cases studied, results of 24-hour ambulatory BP monitoring. VERELAN dosed 240 mg/day (n = 15); placebo (n = 10).[1]



R EDUCES wide variations in BP control[2]

N EGLIGIBLE discontinuation due to side effects[1]

D OSED once daily at all doses

Constipation, which can easily be managed in most patients, is the most frequently reported side effect of verapamil.

Please see brief summary of Prescribing Information including CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS on adjacent page.

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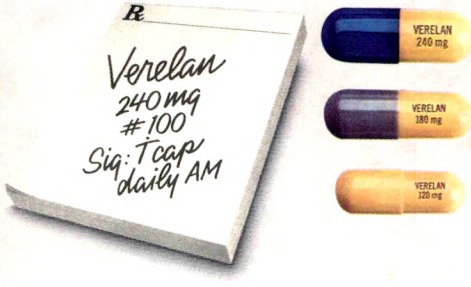
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Verapamil HCl 120 mg 180 mg 240 mg

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ENGINEERED FOR THE CONTROL YOU WANT, THE PROTECTION THEY NEED.

The usual dose is 240 mg once daily. If adequate response is not obtained, the dose may be titrated up to 360 mg or 480 mg once daily. VERELAN 120 mg is available for patients requiring lower-dose verapamil therapy.

References: 1. Carr AA, Bottini PB, Prisant LM, et al. Once-daily verapamil in the treatment of mild-to-moderate hypertension: a double-blind placebo-controlled dose-ranging study. *J Clin Pharmacol.* 1991;31:144-150. **2.** Data on file for VERELAN 240 mg, Lederle Laboratories, Pearl River, NY.

Brief Summary

VERELAN®
Verapamil HCl
Sustained-Release Pellet-Filled Capsules

For complete Prescribing Information, consult package insert.

CLINICAL PHARMACOLOGY

Food does not affect the extent or rate of the absorption of verapamil from the controlled release VERELAN capsule.

Atrioventricular block can occur in patients without preexisting condition defects (see **WARNINGS**).

Acceleration of ventricular rate and/or ventricular fibrillation has been reported in patients with atrial flutter or atrial fibrillation and a coexisting accessory AV pathway following administration of verapamil (see **WARNINGS**).

In patients with hepatic insufficiency, metabolism is delayed and elimination half-life prolonged up to 14 to 16 hours (see **PRECAUTIONS**), the volume of distribution is increased, and plasma clearance reduced to about 30% of normal.

CONTRAINDICATIONS

Severe LV dysfunction (see **WARNINGS**), hypotension (systolic pressure <90 mmHg) or cardiogenic shock, sick sinus syndrome (if no pacemaker is present), second- or third-degree AV block (if no pacemaker is present), atrial flutter/fibrillation with an accessory bypass tract (eg, WPW or LGL syndromes), (see **WARNINGS**), hypersensitivity to verapamil.

WARNINGS

Verapamil should be avoided in patients with severe LV dysfunction (eg, ejection fraction <30%) or moderate-to-severe symptoms of cardiac failure and in patients with any degree of ventricular dysfunction if they are receiving a beta blocker. Control milder heart failure with optimum digitalization and/or diuretics before VERELAN is used. Verapamil may occasionally produce hypotension. Elevations of liver enzymes have been reported.

Several cases of hepatocellular injury have been demonstrated to be produced by verapamil. Periodic monitoring of liver function in patients on verapamil is prudent. Some patients with paroxysmal and/or chronic atrial flutter/fibrillation and an accessory AV pathway (eg, WPW or LGL syndromes) have developed an increased antegrade conduction across the accessory pathway bypassing the AV node, producing a very rapid ventricular response or ventricular fibrillation after receiving IV verapamil (or digitalis). Because of this risk, oral verapamil is contraindicated in such patients. AV block may occur (second- or third-degree, 0.8%). Development of marked first-degree block or progression to second- or third-degree block requires reduction in dosage or, rarely, discontinuation and institution of appropriate therapy. Sinus bradycardia, second-degree AV block, sinus arrest, pulmonary edema and/or severe hypotension were seen in some critically ill patients with hypertrophic cardiomyopathy who were treated with verapamil.

PRECAUTIONS

Verapamil should be given cautiously to patients with impaired hepatic function (in severe dysfunction use about 30% of the normal dose) or impaired renal function, and patients should be monitored for abnormal prolongation of the PR interval or other signs of overdosage. Verapamil may decrease neuromuscular transmission in patients with Duchenne's muscular dystrophy and may prolong recovery from the neuromuscular blocking agent vecuronium. It may be necessary to decrease verapamil dosage in patients with attenuated neuromuscular transmission. Combined therapy with beta-adrenergic blockers and verapamil may result in additive negative effects on heart rate, atrioventricular conduction and/or cardiac contractility; there have been reports of excessive bradycardia and AV block, including complete heart block. The risks of such combined therapy may outweigh the benefits. The combination should be used only with caution and close monitoring. Decreased metoprolol clearance may occur with combined use. Chronic verapamil treatment can

VERELAN® verapamil HCl

increase serum digoxin levels by 50% to 75% during the first week of therapy, which can result in digita toxicity. In patients with hepatic cirrhosis, verapamil may reduce total body clearance and extrarenal cle ance of digitoxin. The digoxin dose should be reduced when verapamil is given and the patient carefu monitored. Verapamil will usually have an additive effect in patients receiving blood pressure-loweri agents. Disopyramide should not be given within 48 hours before or 24 hours after verapamil administratic Concomitant use of flecainide and verapamil may have additive effects on myocardial contractility, AV cc duction, and repolarization. Combined verapamil and quinidine therapy in patients with hypertrophic c diomyopathy should be avoided, since significant hypotension may result. Verapamil has been giv concomitantly with short- and long-acting nitrates without any undesirable drug interactions. Interaction b tween cimetidine and chronically administered verapamil has not been studied. In healthy volunteers, cle ance of verapamil was reduced or unchanged. Concomitant use of lithium and verapamil may result ir lowering of serum lithium levels or increased sensitivity to lithium. Patients receiving both drugs must monitored carefully.

Verapamil may increase carbamazepine concentrations during combined use. Rifampin may reduce ve pamil bioavailability. Phenobarbital may increase verapamil clearance. Verapamil may increase serum le els of cyclosporine. Concomitant use of inhalation anesthetics and calcium antagonists needs care titration to avoid excessive cardiovascular depression. Verapamil may potentiate the activity of neuromusc lar blocking agents (curare-like and depolarizing); dosage reduction may be required. Adequate animal c cinogenicity studies have not been performed. One study in rats did not suggest a tumorigenic potential, a verapamil was not mutagenic in the Ames test. **Pregnancy Category C:** There are no adequate and w controlled studies in pregnant women. This drug should be used during pregnancy, labor, and delivery onl clearly needed. Verapamil is excreted in breast milk; therefore, nursing should be discontinued during ve pamil use. Safety and efficacy of verapamil in children below the age of 18 years have not been establish

ADVERSE REACTIONS

Reversible (upon discontinuation of verapamil) nonobstructive, paralytic ileus has been infrequently ported in association with the use of verapamil.

In clinical trials with 285 hypertensive patients on VERELAN for more than 1 week, the following adve reactions were reported: constipation (7.4%); headache (5.3%); dizziness (4.2%); lethargy (3.2%); dyspe sia (2.5%); rash (1.4%); ankle edema (1.4%); sleep disturbance (1.4%); myalgia (1.1%). In clinical trials other formulations of verapamil HCl (N = 4,954), the following reactions have occurred at rates greater th 1.0%: constipation (7.3%); dizziness (3.3%); nausea (2.7%); hypotension (2.5%); edema (1.9%); headac (2.2%); rash (1.2%); CHF/pulmonary edema (1.8%); fatigue (1.7%); bradycardia (HR<50/min) (1.4%); block-total 1°, 2°, 3° (1.2%); 2° and 3° (0.8%); flushing (0.6%); elevated liver enzymes (see **WARNINGS**)

The following reactions, reported in 1.0% or less of patients, occurred under conditions (open trials, m keting experience) where a causal relationship is uncertain. **Cardiovascular:** angina pectoris, atrioventri lar dissociation, chest pain, claudication, myocardial infarction, palpitations, purpura (vasculitis), synco **Digestive System:** diarrhea, dry mouth, gastrointestinal distress, gingival hyperplasia. **Hemic and Ly phatic:** ecchymosis or bruising. **Nervous System:** cerebrovascular accident, confusion, equilibrium dis ders, insomnia, muscle cramps, paresthesia, psychotic symptoms, shakiness, somnolence. **Respirato** dyspnea. **Skin:** arthralgia and rash, exanthema, hair loss, hyperkeratosis, maculae, sweating, urtica Stevens-Johnson syndrome, erythema multiforme. **Special Senses:** blurred vision. **Urogenital:** gyne mastia, impotence, increased urination, spotty menstruation.

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events in clinically healthy older subjects; silent ischemia, although infrequent, may be the best predictor of future coronary events in such a population.

752

Effect of High-Current Stimulation in Patients with Sustained Ventricular Tachycardia Rendered Noninducible by Antiarrhythmic Drugs

Bruce G. Hook, Francis E. Marchlinski, Mark E. Josephson, and Alfred E. Buxton

Successful antiarrhythmic drug therapy for sustained ventricular tachycardia (VT) is presumed to be related to effects on myocardium within the reentrant circuit. To test the hypothesis that prevention of VT induction may be related to effects on myocardium other than that directly involved in the tachycardia circuit, high-current stimulation was used to achieve shorter coupling intervals in 22 patients with sustained uniform VT that was rendered noninducible by antiarrhythmic agents during stimulation at twice threshold. Sustained uniform VT was induced in 10 patients in response to high-current stimulation (group 1), including 4 tachycardias with the same morphology observed in the baseline study. There were no inducible arrhythmias in 12 patients (group 2). There was no statistically significant difference between groups 1 and 2 in baseline VT cycle length, drug-induced increase in effective refractory period, QRS duration or maximal current strength delivered. Thus, limiting the prematurity of extrastimuli achieved at the tachycardia circuit may be one mechanism by which antiarrhythmic drugs prevent induction of VT during programmed stimulation.

758

Reproducibility of Programmed Electrical Stimulation Responses in Patients with Ventricular Tachycardia or Fibrillation Associated with Coronary Artery Disease

Annabelle S. Volgman, Terry A. Zheutlin, Thomas A. Mattioni, Michele A. Parker, and Richard F. Kehoe

Patients with sustained ventricular tachycardia (VT) or fibrillation were studied using an aggressive programmed electrical stimulation (PES) protocol (n = 102). The PES study was repeated to confirm PES responses. Patients with coronary artery disease (n = 72) were identified and results of these patients were analyzed and compared with results of patients without coronary artery disease. No significant difference in concordance of PES responses was found in the 2 groups of patients. PES responses of noninducible and sustained VT were more reproducible than nonsustained VT. PES response of sustained monomorphic VT was more reproducible than polymorphic VT. Induction of rapid sustained VT was less reproducible than induction of a slower sustained VT. It is recommended that PES end points of nonsustained, polymorphous and rapid VT not be used to guide antiarrhythmic therapy.

765
Late Ventricular Arrhythmia and Sudden Death Following Direct-Current Catheter Ablation of the Atrioventricular Junction
James C. Perry, Debra L. Kearney, Richard A. Friedman, Jeffrey P. Moak, and Arthur Garson, Jr.

Nine patients underwent direct-current catheter ablation (DCCA) of the atrioventricular (AV) junction at Texas Children's Hospital 4 to 9 years ago: 3 patients had DCCA in the coronary sinus for permanent junctional reciprocating tachycardia, 2 patients had His ablation, 2 had coronary sinus and His ablation for permanent junctional reciprocating tachycardia, and 2 had DCCA for congenital junctional ectopic tachycardia. During follow-up, 3 patients developed clinical ventricular tachycardia: all 3 had DCCA of the His bundle. One asymptomatic patient with ventricular tachycardia died suddenly 6 years after DCCA with ventricular fibrillation. Autopsy revealed 2 ventricular scars: 1 extending from the AV junction and 1 in the outflow tract. No patient with DCCA limited to the coronary sinus developed ventricular tachycardia. DCCA of the bundle of His can result in late ventricular arrhythmias, possibly as a result of extension of the DCCA lesion into the ventricle. These late findings should be considered in evaluating the safety, efficacy and follow-up for patients undergoing radiofrequency ablation.

VALVULAR HEART DISEASE

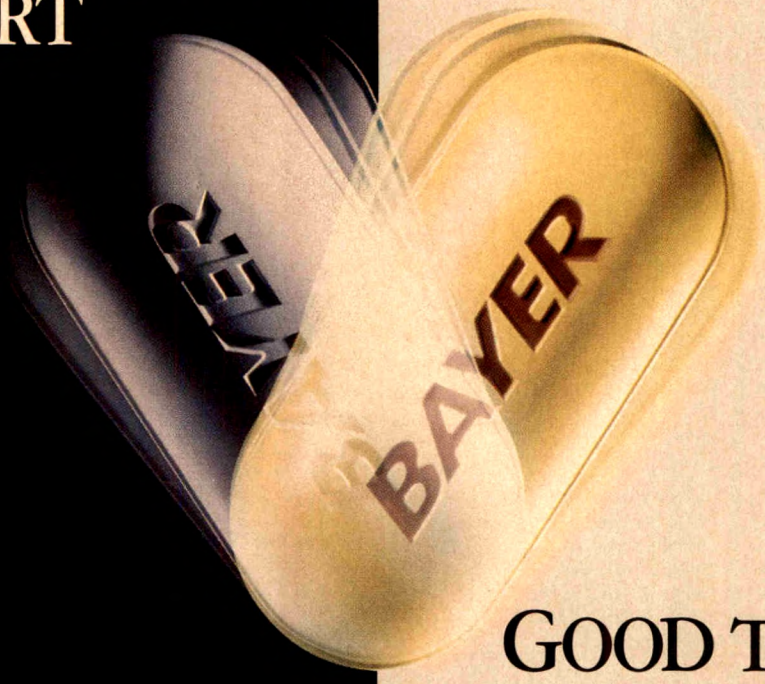
769
Reappraisal by Transesophageal Echocardiography of the Significance of Left Atrial Thrombi in the Prediction of Systemic Arterial Embolization in Rheumatic Mitral Valve Disease
Juey-Jen Hwang, Peiliang Kuan, Shen-Chang Lin, Wei-Jan Chen, Meng-Huan Lei, Yu-Lin Ko, Jun-Jack Cheng, Jiunn-Lee Lin, Jin-Jer Chen, and Wen-Pin Lien

Transesophageal echocardiography was used to study the association of left atrial thrombosis with systemic arterial embolization (either recent or remote) in 260 consecutive patients with rheumatic mitral valve disease during a period of 24 months. It is concluded that: (1) patients with left atrial thrombi were at significantly higher risk for systemic arterial embolization than were those without them, and this association was not dependent on the timing of the embolic events; (2) transesophageal echocardiography is a convenient and accurate diagnostic modality to identify this high-risk group; and (3) preventive anticoagulant therapy for possible embolic complications should be more vigorously adhered to in such patients.

Continued on page A31

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Safety-coated Therapy BAYER® ENTERIC: An ideal choice for second MI prophylaxis.

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Please see Brief Summary of Prescribing Information on the following page.

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BRIEF SUMMARY

Therapy BAYER® ENTERIC Aspirin

Delayed-Release Enteric Aspirin (Acetylsalicylic Acid) Caplets to Help Reduce the Risk of Second MI or MI in Unstable Angina

DOSAGE AND ADMINISTRATION:

Although most of the studies used dosages exceeding 300 mg, two trials used only 300 mg daily, and pharmacologic data indicate that this dose inhibits platelet function fully. Therefore, 300 mg or a conventional 325 mg aspirin dose daily is a reasonable routine dose that would minimize gastrointestinal adverse reactions. This use of aspirin applies to both solid oral dosage forms (buffered and plain aspirin) and buffered aspirin in solution.

CARDIOVASCULAR AND BIOCHEMICAL:

In the AMIS trial, the dosage of 1,000 mg per day of aspirin was associated with small increases in systolic blood pressure (BP) (average 1.5 to 2.1 mm) and diastolic BP (0.5 to 0.6 mm), depending upon whether maximal or last available readings were used. Blood urea nitrogen and uric acid levels were also increased but by less than 1.0 mg percent. Subjects with marked hypertension or renal insufficiency had been excluded from the trial so that the clinical importance of these observations for such subjects or for any subjects treated over more prolonged periods is not known. It is recommended that patients placed on long-term aspirin treatment, even at doses of 300 mg per day, be seen at regular intervals to assess changes in these measurements.

BIOAVAILABILITY:

A single-dose bioavailability study[1] has demonstrated that plasma acetylsalicylic acid and salicylic acid concentrations resulting from Therapy BAYER® ENTERIC are equivalent to those from plain aspirin, i.e., non-enteric-coated aspirin. As expected, the enteric coating on Therapy BAYER® ENTERIC results in delayed absorption (peak achieved at approximately five hours postdosing) relative to plain aspirin. Dissolution of the enteric coating occurs at neutral-to-basic pH and is therefore dependent on gastric emptying into the duodenum. With continued dosing, appropriate therapeutic plasma levels are maintained.

SAFETY:

The safety of enteric-coated aspirin has been demonstrated in a number of endoscopic studies comparing enteric-coated aspirin and plain aspirin, as well as plain buffered and "arthritis strength" preparations. In these studies, endoscopies were performed in healthy volunteers before and after either two-day or 14-day administration of aspirin doses of 3,900 or 4,000 mg per day. Compared to all the other preparations, the enteric-coated aspirin produced significantly less damage to the gastric mucosa. There was also statistically less duodenal damage when compared with the plain, i.e., non-enteric-coated, aspirin.

ADVERSE REACTIONS:

Gastrointestinal reactions: Doses of 1,000 mg per day of aspirin caused gastrointestinal symptoms and bleeding that, in some cases, were clinically significant. In the largest postinfarction study (the Aspirin Myocardial Infarction Study [AMIS] with 4,500 people),[2] the percentage of incidences of gastrointestinal symptoms for the aspirin (1,000 mg of a standard, solid-tablet formulation) and placebo-treated subjects, respectively, were stomach pain (14.5%, 4.4%), heartburn (11.9%, 4.8%), nausea and/or vomiting (7.6%, 2.1%), and hospitalization for GI disorder (4.9%, 3.5%). In the AMIS and other trials, aspirin-treated patients had increased rates of gross gastrointestinal bleeding. Symptoms and signs of gastrointestinal irritation were not significantly increased in subjects treated for unstable angina with buffered aspirin in solution.

PROFESSIONAL WARNING:

Occasional reports have documented individuals with impaired gastric emptying in whom there may be retention of one or more enteric-coated aspirin caplets over time. This phenomenon may occur as a result of outlet obstruction from ulcer disease alone or combined with hypotonic gastric peristalsis. Because of the integrity of the enteric coating in an acidic environment, these caplets may accumulate and form a bezoar in the stomach. Individuals with this condition may present with complaints of early satiety or of vague upper abdominal distress. Diagnosis may be made by endoscopy or by abdominal films, which show opacities suggestive of a mass of small caplets.[3] Management may vary according to the condition of the patient. Options include gastrotomy and alternating slightly basic and neutral lavage.[4] While there have been no clinical reports, it has been suggested that such individuals may also be treated with parenteral cimetidine (to reduce acid secretion) and then given sips of slightly basic liquids to effect gradual dissolution of the enteric coating. Progress may be followed with plasma salicylate levels or via recognition of tinnitus by the patient.

It should be kept in mind that individuals with a history of partial or complete gastrectomy may produce reduced amounts of acid and therefore have less acidic gastric pH. Under these circumstances, the benefits offered by the acid-resistant enteric coating may not exist.

REFERENCES:

1. Data on file, Sterling Health. 2. Aspirin Myocardial Infarction Study Research Group: A randomized, controlled trial of aspirin in persons recovered from myocardial infarction. *JAMA* 1980;245:661-669. 3. Bogacz K, Caldron P: Enteric-coated aspirin bezoar: Elevation of serum salicylate level by barium study. *Am J Med* 1987;83:783-786. 4. Baum J: Enteric-coated aspirin and the problem of gastric retention. *J Rheumatol* 1984;11:250-251.

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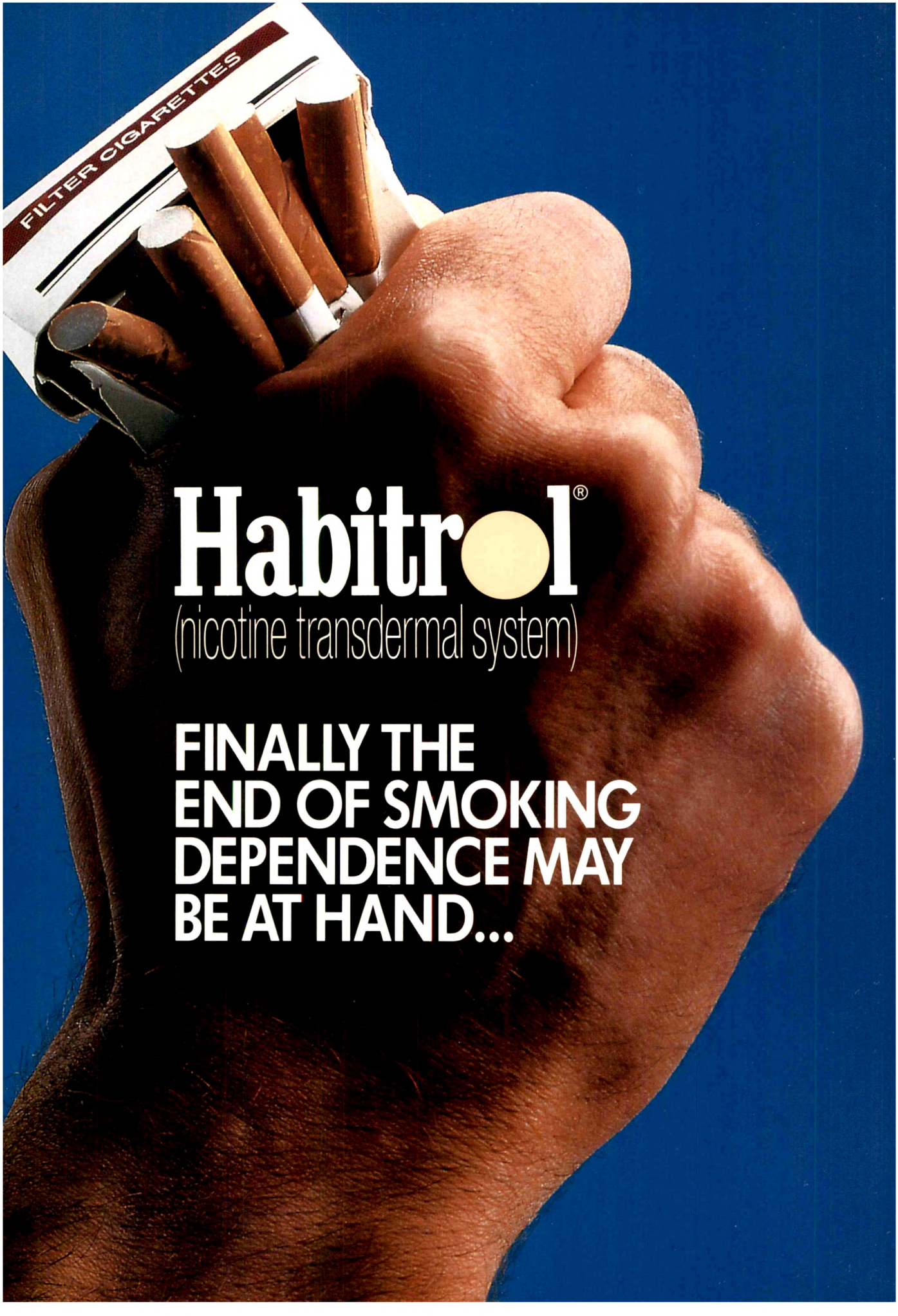
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FILTER CIGARETTES
Habitrol®
(nicotine transdermal system)
FINALLY THE
END OF SMOKING
DEPENDENCE MAY
BE AT HAND...

For the motivated patient who wants to quit

Habitrol®

(nicotine transdermal system)



Habitrol significantly increases abstinence rates* when used as part of a comprehensive behavioral smoking cessation program—even in moderately to highly nicotine-dependent patients[1†]

- Significantly reduces craving for cigarettes through controlled nicotine release[1]
- Helps break the chain of smoking dependence with full 24-hour nicotine plasma levels
- Safe and well tolerated
- Provides the safety of child-resistant packaging

Habitrol is available with a Patient Support Kit, to be used as part of a comprehensive behavioral smoking cessation program. This kit provides materials to help motivated patients address the behavioral and social components of smoking dependence.

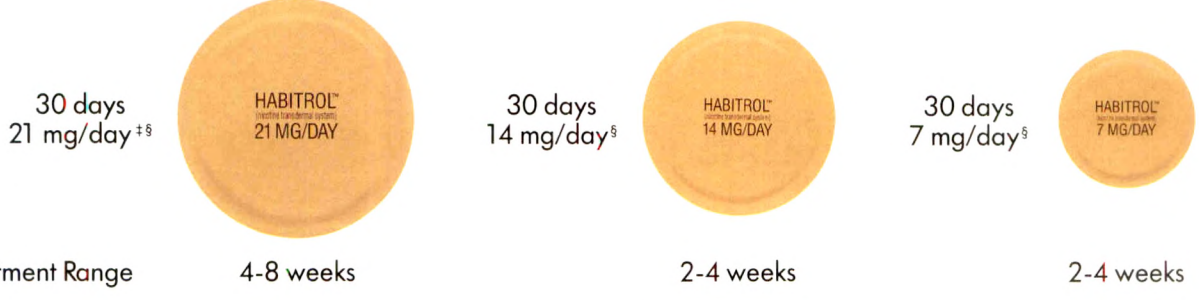
This product should not be used for more than three months. The effects of Habitrol treatment on fetal development are unknown. Pregnant or nursing smokers should be encouraged to attempt smoking cessation using nonpharmacologic approaches before using Habitrol. The risks vs. benefits of nicotine replacement should be weighed in patients with certain cardiovascular and peripheral vascular diseases. Certain concomitant medications may need dosage adjustments (see Drug Interactions section of complete Prescribing Information).

THE PATCH THAT BEATS THE PACK

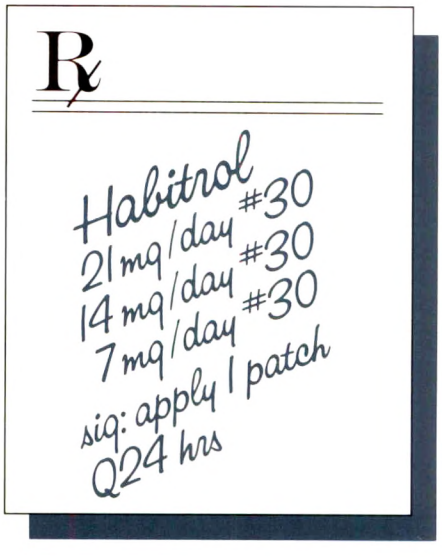


Helps patients adjust to a smokefree life-style with gradual reduction of nicotine

- Available in three dosages for step-down therapy
- Start most patients on one 21 mg/day patch for 30 days, continue with one 14 mg/day patch for 30 days, and follow with one 7 mg/day patch for 30 days‡



- Used and unused systems should be kept out of the reach of children and pets



*Abstinence was measured by diary entries and confirmed by breath carbon monoxide levels.
†Represents patients scoring ≥6 points on the Fagerstrom Tolerance Test
‡For patients with coronary artery disease or who weigh less than 100 lbs or smoke less than ½ pack of cigarettes/day, please see Individualization of Dosage Section of Prescribing Information
§Patches shown 50% of actual size

Please see brief summary of Prescribing Information on next page.

Habitrol™

(nicotine transdermal system) Systemic delivery of 21, 14, or 7 mg/day over 24 hours

BRIEF SUMMARY (FOR FULL PRESCRIBING INFORMATION, SEE PACKAGE INSERT)

INDICATIONS AND USAGE

Habitrol treatment is indicated as an aid to smoking cessation for the relief of nicotine withdrawal symptoms. Habitrol treatment should be used as a part of a comprehensive behavioral smoking cessation program.

The use of Habitrol systems for longer than 3 months has not been studied.

CONTRAINDICATIONS

Use of Habitrol systems is contraindicated in patients with hypersensitivity or allergy to nicotine or to any of the components of the therapeutic system.

WARNINGS

Nicotine from any source can be toxic and addictive. Smoking causes lung cancer, heart disease, emphysema, and may adversely affect the fetus and the pregnant woman. For any smoker, with or without concomitant disease or pregnancy, the risk of nicotine replacement in a smoking cessation program should be weighed against the hazard of continued smoking while using Habitrol systems, and the likelihood of achieving cessation of smoking without nicotine replacement.

Pregnancy Warning

Tobacco smoke, which has been shown to be harmful to the fetus, contains nicotine, hydrogen cyanide, and carbon monoxide. Nicotine has been shown in animal studies to cause fetal harm. It is therefore presumed that Habitrol treatment can cause fetal harm when administered to a pregnant woman. The effect of nicotine delivery by Habitrol systems has not been examined in pregnancy (see PRECAUTIONS, Other Effects). Therefore pregnant smokers should be encouraged to attempt cessation using educational and behavioral interventions before using pharmacological approaches. If Habitrol therapy is used during pregnancy, or if the patient becomes pregnant while using Habitrol treatment, the patient should be apprised of the potential hazard to the fetus.

Safety Note Concerning Children

The amounts of nicotine that are tolerated by adult smokers can produce symptoms of poisoning and could prove fatal if Habitrol systems are applied or ingested by children or pets. Used 21 mg/day systems contain about 60% (32 mg) of their initial drug content. Therefore, patients should be cautioned to keep both used and unused Habitrol systems out of the reach of children and pets.

PRECAUTIONS

General

The patient should be urged to stop smoking completely when initiating Habitrol therapy (see DOSAGE AND ADMINISTRATION). Patients should be informed that if they continue to smoke while using Habitrol systems, they may experience adverse effects due to peak nicotine levels higher than those experienced from smoking alone. If there is a clinically significant increase in cardiovascular or other effects attributable to nicotine, the Habitrol dose should be reduced or Habitrol treatment discontinued (see WARNINGS). Physicians should anticipate that concomitant medications may need dosage adjustment (see Drug Interactions).

The use of Habitrol systems beyond 3 months by patients who stop smoking should be discouraged because the chronic consumption of nicotine by any route can be harmful and addicting.

Allergic Reactions: In a 6-week open-label dermal irritation and sensitization study of Habitrol systems, 22 of 220 patients exhibited definite erythema at 24 hours after application. Upon rechallenge, 3 patients exhibited mild-to-moderate contact allergy. Patients with contact sensitization should be cautioned that a serious reaction could occur from exposure to other nicotine-containing products or smoking. In the efficacy trials, erythema following system removal was typically seen in about 17% of patients, some edema in 4%, and dropouts due to skin reactions occurred in 6% of patients.

Patients should be instructed to promptly discontinue the Habitrol treatment and contact their physicians if they experience severe or persistent local skin reactions at the site of application (e.g., severe erythema, pruritus or edema) or a generalized skin reaction (e.g., urticaria, hives, or generalized rash).

Skin Disease: Habitrol systems are usually well tolerated by patients with normal skin, but may be irritating for patients with some skin disorders (atopic or eczematous dermatitis).

Cardiovascular or Peripheral Vascular Diseases: The risks of nicotine replacement in patients with certain cardiovascular and peripheral vascular diseases should be weighed against the benefits of including nicotine replacement in a smoking cessation program for them. Specifically, patients with coronary heart disease (history of myocardial infarction and/or angina pectoris), serious cardiac arrhythmias, or vasospastic diseases (Buerger's disease, Prinzmetal's variant angina) should be carefully screened and evaluated before nicotine replacement is prescribed.

Tachycardia occurring in association with the use of Habitrol treatment was reported occasionally. If serious cardiovascular symptoms occur with Habitrol treatment, it should be discontinued.

Habitrol treatment should generally not be used in patients during the immediate post-myocardial infarction period, patients with serious arrhythmias, and patients with severe or worsening angina pectoris.

Renal or Hepatic Insufficiency: The pharmacokinetics of nicotine have not been studied in the elderly or in patients with renal or hepatic impairment. However, given that nicotine is extensively metabolized and that its total system clearance is dependent on liver blood flow, some influence of hepatic impairment on drug kinetics (reduced clearance) should be anticipated. Only severe renal impairment would be expected to affect the clearance of nicotine or its metabolites from the circulation (see CLINICAL PHARMACOLOGY, Pharmacokinetics).

Endocrine Diseases: Habitrol treatment should be used with caution in patients with hyperthyroidism, pheochromocytoma or insulin-dependent diabetes since nicotine causes the release of catecholamines by the adrenal medulla.

Peptic Ulcer Disease: Nicotine delays healing in peptic ulcer disease; therefore, Habitrol treatment should be used with caution in patients with active peptic ulcers and only when the benefits of including nicotine replacement in a smoking cessation program outweigh the risks.

Accelerated Hypertension: Nicotine constitutes a risk factor for development of malignant hypertension in patients with accelerated hypertension; therefore, Habitrol treatment should be used with caution in these patients and only when the benefits of including nicotine replacement in a smoking cessation program outweigh the risks.

Information for Patients

A patient instruction sheet is included in the package of Habitrol systems dispensed to the patient. It contains important information and instructions on how to use and dispose of Habitrol systems properly. Patients should be encouraged to ask questions of the physician and pharmacist.

Patients must be advised to keep both used and unused systems out of the reach of children and pets.

Drug Interactions

Smoking cessation, with or without nicotine replacement, may alter the pharmacokinetics of certain concomitant medications.

May Require a Decrease in Dose at Cessation of Smoking	Possible Mechanism
Acetaminophen, caffeine, imipramine, oxazepam, pentazocine, propranolol, theophylline	Deinduction of hepatic enzymes on smoking cessation
Insulin	Increase of subcutaneous insulin absorption with smoking cessation
Adrenergic antagonists (e.g., prazosin, labetalol)	Decrease in circulating catecholamines with smoking cessation

May Require an Increase in Dose at Cessation of Smoking	Possible Mechanism
Adrenergic agonists (e.g., isoproterenol, phenylephrine)	Decrease in circulating catecholamines with smoking cessation

Carcinogenesis, Mutagenesis, Impairment of Fertility

Nicotine itself does not appear to be a carcinogen in laboratory animals. However, nicotine and its metabolites increased the incidence of tumors in the cheek pouches of hamsters and forestomach of F344 rats, respectively, when given in combination with tumor-initiators. One study, which could not be replicated, suggested that cotinine, the primary metabolite of nicotine, may cause lymphoreticular sarcoma in the large intestine in rats.

Nicotine and cotinine were not mutagenic in the Ames *Salmonella* test. Nicotine induced repairable DNA damage in an *E. coli* test system. Nicotine was shown to be genotoxic in a test system using Chinese hamster ovary cells. In rats and rabbits, implantation can be delayed or inhibited by a reduction in DNA synthesis that appears to be caused by nicotine. Studies have shown a decrease in litter size in rats treated with nicotine during gestation.

Pregnancy Category D (see WARNINGS)

The harmful effects of cigarette smoking on maternal and fetal health are clearly established. These include low birth weight, an increased risk of spontaneous abortion, and increased perinatal mortality. The specific effects of Habitrol treatment on fetal development are unknown. Therefore, pregnant smokers should be encouraged to attempt cessation using educational and behavioral interventions before using pharmacological approaches.

Spontaneous abortion during nicotine replacement therapy has been reported; as with smoking, nicotine as a contributing factor cannot be excluded.

Habitrol treatment should be used during pregnancy only if the likelihood of smoking cessation justifies the potential risk of use of nicotine replacement by the patient, who may continue to smoke.

Teratogenicity

Animal Studies: Nicotine was shown to produce skeletal abnormalities in the offspring of mice when given doses toxic to the dams (25 mg/kg/day IP or SC).

Human Studies: Nicotine teratogenicity has not been studied in humans except as a component of cigarette smoke (each cigarette smoked delivers about 1 mg of nicotine). It has not been possible to conclude whether cigarette smoking is teratogenic to humans.

Other Effects

Animal Studies: A nicotine bolus (up to 2 mg/kg) to pregnant rhesus monkeys caused acidosis, hypercarbia, and hypotension (fetal and maternal concentrations were about 20 times those achieved after smoking 1 cigarette in 5 minutes). Fetal breathing movements were reduced in the fetal lamb after intravenous injection of 0.25 mg/kg nicotine to the ewe (equivalent to smoking 1 cigarette every 20 seconds for 5 minutes). Uterine blood flow was reduced about 30% after infusion of 0.1 mg/kg/min nicotine for 20 minutes to pregnant rhesus monkeys (equivalent to smoking about six cigarettes every minute for 20 minutes).

Human Experience: Cigarette smoking during pregnancy is associated with an increased risk of spontaneous abortion, low-birth-weight infants and perinatal mortality. Nicotine and carbon monoxide are considered the most likely mediators of these outcomes. The effects of cigarette smoking on fetal cardiovascular parameters has been studied near term. Cigarettes increased fetal aortic blood flow and heart rate, and decreased uterine blood flow and fetal breathing movements. Habitrol treatment has not been studied in pregnant humans.

Labor and Delivery

Habitrol systems are not recommended to be left on during labor and delivery. The effects of nicotine on the mother or the fetus during labor are unknown.

Nursing Mothers

Caution should be exercised when Habitrol therapy is administered to nursing women. The safety of Habitrol treatment in nursing infants has not been examined. Nicotine passes freely into breast milk; the milk-to-plasma ratio averages 2.9. Nicotine is absorbed orally. An infant has the ability to clear nicotine by hepatic first-pass clearance; however, the efficiency of removal is probably lowest at birth. The nicotine concentrations in milk can be expected to be lower with Habitrol treatment when used as directed than with cigarette smoking, as maternal plasma nicotine concentrations are generally reduced with nicotine replacement. The risk of exposure of the infant to nicotine from Habitrol systems should be weigh against the risks associated with the infant's exposure to nicot from continued smoking by the mother (passive smoke expos and contamination of breast milk with other components tobacco smoke) and from Habitrol systems alone or in combinat with continued smoking.

Pediatric Use

Habitrol systems are not recommended for use in children beca the safety and effectiveness of Habitrol treatment in children adolescents who smoke have not been evaluated.

Geriatric Use

Forty-eight patients over the age of 60 participated in clinical tr of Habitrol therapy. Habitrol therapy appeared to be as effectiv this age group as in younger smokers.

ADVERSE REACTIONS

Assessment of adverse events in the 792 patients who participa in controlled clinical trials is complicated by the occurrence of and CNS effects of nicotine withdrawal as well as nicotine exc The actual incidences of both are confounded by concurrent sm ing by many of the patients. In the trials, when reporting adve events, the investigators did not attempt to identify the cause of symptom.

Topical Adverse Events

The most common adverse event associated with topical nicotin a short-lived erythema, pruritus, or burning at the application s which was seen at least once in 35% of patients on Habitrol tre ment in the clinical trials. Local erythema after system removal noted at least once in 17% of patients and local edema in 4%. E thema generally resolved within 24 hours. Cutaneous hyperse tivity (contact sensitization) occurred in 2% of patients on Habi treatment (see PRECAUTIONS, Allergic Reactions).

Probably Causally Related

The following adverse events were reported more frequentl Habitrol-treated patients than in placebo-treated patients exhibited a dose response in clinical trials.

Digestive system – Diarrhea,* dyspepsia.*
Mouth/Tooth disorders – Dry mouth.
Musculoskeletal system – Arthralgia,* myalgia.*
Nervous system – Abnormal dreams,† somnolence.†

Frequencies for 21 mg/day system
*Reported in 3% to 9% of patients.
†Reported in 1% to 3% of patients.
Unmarked if reported in <1% of patients.

Causal Relationship Unknown

Adverse events reported in Habitrol- and placebo-treated patie at about the same frequency in clinical trials are listed below. clinical significance of the association between Habitrol treatm and these events is unknown, but they are reported as alert information for the clinician.

Body as a whole – Allergy,† back pain.†
Cardiovascular system – Hypertension.†
Digestive system – Abdominal pain,† constipation,† nause vomiting.
Nervous system – Dizziness,* concentration impaired,† headache (17%), insomnia.*
Respiratory system – Cough increased,† pharyngitis,† sinusitis.†
Urogenital system – Dysmenorrhea.*

Frequencies for 21 mg/day system
*Reported in 3% to 9% of patients.
†Reported in 1% to 3% of patients.
Unmarked if reported in <1% of patients.

DRUG ABUSE AND DEPENDENCE

Habitrol systems are likely to have a low abuse potential based differences between it and cigarettes in four characteristics c monly considered important in contributing to abuse: much slo absorption, much smaller fluctuations in blood levels, lower bl levels of nicotine, and less frequent use (i.e. once daily).

Dependence on nicotine polacrilex chewing gum replacem therapy has been reported. Such dependence might also oc from transference to Habitrol systems of tobacco-based nico dependence. The use of the system beyond 3 months has not b evaluated and should be discouraged.

To minimize the risk of dependence, patients should be enc aged to withdraw gradually from Habitrol treatment after 8 weeks of usage. Recommended dose reduction is to progressi decrease the dose every 2 to 4 weeks (see DOSAGE AND ADM ISTRATION).

CAUTION: Federal law prohibits dispensing without prescript

C92-1 (Rev. 2

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1. Data on file, Basel Pharmaceuticals.

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774
Usefulness of Left Atrial and Left Ventricular Chamber Sizes as Predictors of the Severity of Mitral Regurgitation
Ian G. Burwash, Gail L. Blackmore, and Chris J. Koilpillai

Left atrial (LA) and left ventricular (LV) chamber dimensions were studied in 92 patients with angiographic and echocardiographic mitral regurgitation (MR) to determine their ability to identify severe regurgitation in the diverse clinical settings in which MR occurs. Atrial dimensions provided the best discriminator but were accurate only in the subgroup of patients with isolated chronic MR with preserved LV function and sinus rhythm. In these patients an LA volume >58 ml, anteroposterior dimension >45 mm and superoinferior dimension >55 mm had high sensitivities (75, 75 and 88%), specificities (83, 100 and 83%) and positive predictive values (92, 100 and 93%), but lower negative predictive values (56, 60 and 71%), respectively. Normalizing dimensions for body surface area was not helpful. LV dimensions had lower sensitivities when specificities and positive predictive values were equivalent. When MR was acute or associated with atrial fibrillation, LV dysfunction or other valvular disease, chamber dimensions were unreliable markers of MR severity.

780
Pulmonary Venous Flow Dynamics Before and After Balloon Mitral Valvuloplasty as Determined by Transesophageal Doppler Echocardiography
Neeraj Jolly, Ramesh Arora, Jagdish C. Mohan, and Mohammed Khalilullah

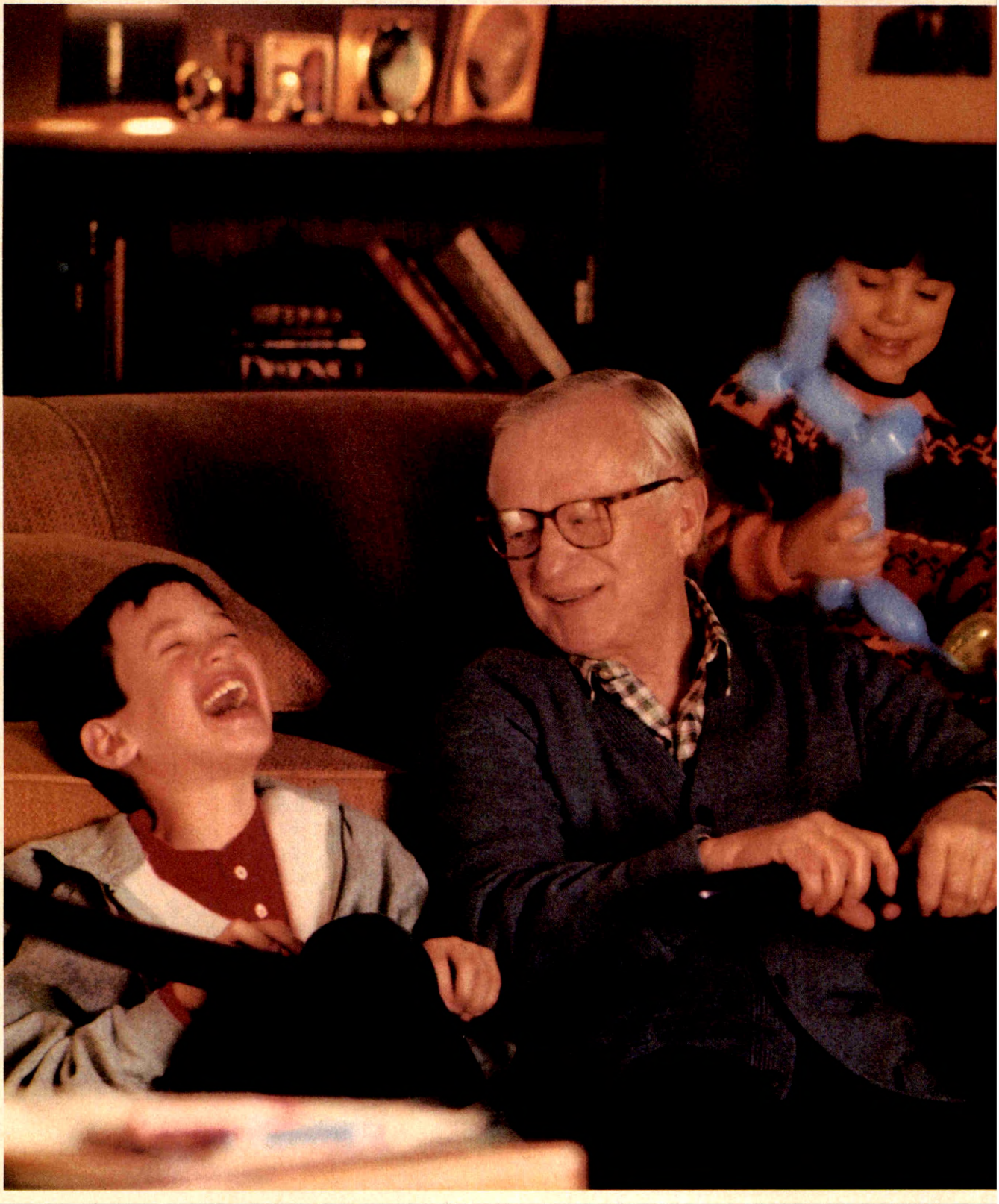
Pulmonary venous flow dynamics in 14 patients with severe mitral stenosis in sinus rhythm, and the acute effect of successful balloon mitral valvuloplasty on these parameters were evaluated. Patients in the basal state had biphasic left atrial filling. A significant increase in mitral valve orifice area was associated with increases in peak systolic forward flow velocity (35 ± 16 to 44 ± 10 cm/s; $p < 0.01$), systolic flow velocity time integral (3.3 ± 1.5 to 5.9 ± 2.0 cm; $p < 0.001$) and the ratio of systolic/diastolic forward flow velocity time integrals (0.8 ± 0.4 to 1.4 ± 0.5; $p < 0.001$). No change in diastolic forward flow peak velocity or its time integral was observed. The relief in mitral valve obstruction results in an increase in the systolic phase of left atrial filling by the interaction of several variables.

CARDIOMYOPATHY

785
Relation Between Extent of Cardiac Muscle Cell Disorganization and Left Ventricular Wall Thickness in Hypertrophic Cardiomyopathy
Barry J. Maron, James K. Wolfson, and William C. Roberts

The presence of numerous, abnormally arranged, cardiac muscle cells distributed widely throughout the hypertrophied left ventricular (LV) wall has been considered a characteristic, morphologic feature of patients dying of hypertrophic cardiomyopathy and also probably a determinant of

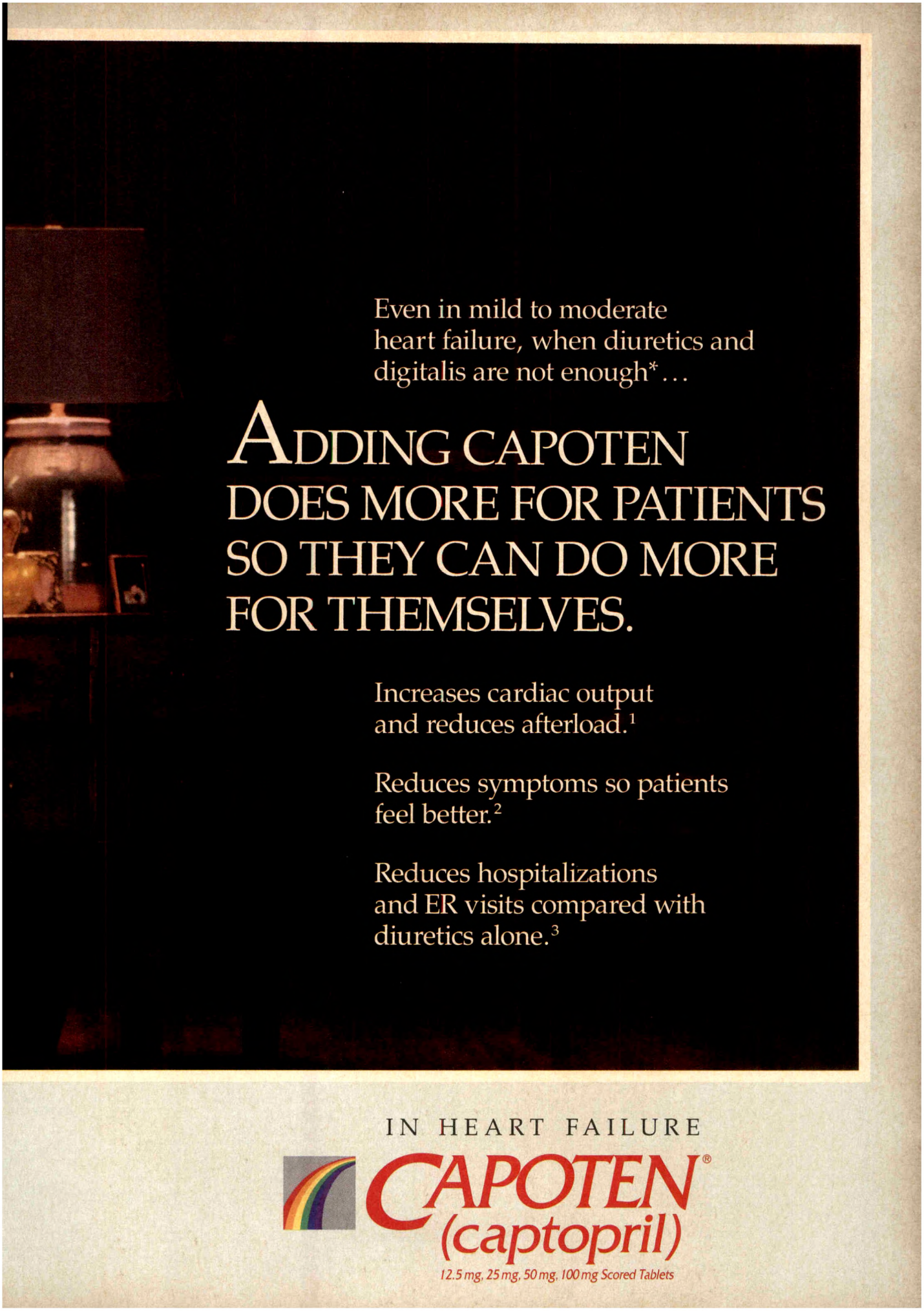
Continued on page A35



CAPOTEN is contraindicated in patients who are hypersensitive to this product. Angioedema has been reported in patients receiving ACE inhibitors.

***CAPOTEN should generally be added to diuretics and digitalis except when digitalis use is poorly tolerated or otherwise not feasible; add CAPOTEN when patients have not responded adequately.**

Please see brief summary, including the **boxed WARNING regarding Use in Pregnancy,** on the last page of this ad.


Even in mild to moderate heart failure, when diuretics and digitalis are not enough*...
ADDING CAPOTEN DOES MORE FOR PATIENTS SO THEY CAN DO MORE FOR THEMSELVES.
Increases cardiac output and reduces afterload.[1]
Reduces symptoms so patients feel better.[2]
Reduces hospitalizations and ER visits compared with diuretics alone.[3]
IN HEART FAILURE
CAPOTEN®
(captopril)
12.5 mg, 25 mg, 50 mg, 100 mg Scored Tablets

CAPOTEN® TABLETS
Captopril Tablets

USE IN PREGNANCY

When used in pregnancy during the second and third trimesters, ACE inhibitors can cause injury and even death to the developing fetus. When pregnancy is detected, CAPOTEN should be discontinued as soon as possible. **See WARNINGS: Fetal/Neonatal Morbidity and Mortality.**

CONTRAINDICATIONS: CAPOTEN is contraindicated in patients who are hypersensitive to this product or any other angiotensin-converting enzyme inhibitor (e.g., a patient who has experienced angioedema during therapy with any other ACE inhibitor).

WARNINGS: Angioedema: Angioedema involving the extremities, face, lips, mucous membranes, tongue, glottis or larynx has been seen in patients treated with ACE inhibitors, including captopril. If angioedema involves the tongue, glottis or larynx, airway obstruction may occur and be fatal. Emergency therapy, including but not necessarily limited to, subcutaneous administration of a 1:1000 solution of epinephrine should be promptly instituted.

Neutropenia / Agranulocytosis: Neutropenia ($<1000/mm^3$) with myeloid hypoplasia has resulted from use of captopril. About half of the neutropenic patients developed systemic or oral cavity infections or other features of the syndrome of agranulocytosis. The risk of neutropenia is dependent on the clinical status of the patient:

In clinical trials in patients with hypertension who have normal renal function (serum creatinine less than 1.6 mg/dL and no collagen vascular disease), neutropenia has been seen in one patient out of over 8,600 exposed. In patients with some degree of renal failure (serum creatinine at least 1.6 mg/dL) but no collagen vascular disease, the risk in clinical trials was about 1 per 500. Doses were relatively high in these patients, particularly in view of their diminished renal function. In patients with collagen vascular diseases (e.g., systemic lupus erythematosus, scleroderma) and impaired renal function, neutropenia occurred in 3.7% of patients in clinical trials. While none of the over 750 patients in formal clinical trials of heart failure developed neutropenia, it has occurred during the subsequent clinical experience. Of reported cases, about half had serum creatinine $\geq$ 1.6 mg/dL and more than 75% received procainamide. In heart failure, it appears that the same risk factors for neutropenia are present.

Neutropenia has appeared usually within 3 months after starting therapy, associated with myeloid hypoplasia and frequently accompanied by erythroid hypoplasia and decreased numbers of megakaryocytes (e.g., hypoplastic bone marrow and pancytopenia); anemia and thrombocytopenia were sometimes seen. Neutrophils generally returned to normal in about 2 weeks after captopril was discontinued, and serious infections were limited to clinically complex patients. About 13% of the cases of neutropenia have ended fatally, but almost all fatalities were in patients with serious illness, having collagen vascular disease, renal failure, heart failure or immunosuppressant therapy, or a combination of these complicating factors. **Evaluation of the hypertensive or heart failure patient should always include assessment of renal function.** If captopril is used in patients with impaired renal function, white blood cell and differential counts should be evaluated prior to starting treatment and at approximately 2-week intervals for about 3 months, then periodically. In patients with collagen vascular disease or who are exposed to other drugs known to affect the white cells or immune response, particularly when there is impaired renal function, captopril should be used only after an assessment of benefit and risk, and then with caution. All patients treated with captopril should be told to report any signs of infection (e.g., sore throat, fever). If infection is suspected, perform white cell counts without delay. Since discontinuation of captopril and other drugs has generally led to prompt return of the white count to normal, upon confirmation of neutropenia (neutrophil count $<1000/mm^3$) withdraw captopril and closely follow the patient's course.

Proteinuria: Total urinary proteins >1 g per day were seen in about 0.7% of patients on captopril. About 90% of affected patients had evidence of prior renal disease or received high doses (>150 mg/day), or both. The nephrotic syndrome occurred in about one-fifth of proteinuric patients. In most cases, proteinuria subsided or cleared within 6 months whether or not captopril was continued. The BUN and creatinine were seldom altered in proteinuric patients. Since most cases of proteinuria occurred by the 8th month of therapy with captopril, patients with prior renal disease or those receiving captopril at doses >150 mg per day, should have urinary protein estimates (dip-stick on 1st morning urine) before therapy, and periodically thereafter.

Hypotension: Excessive hypotension was rarely seen in hypertensive patients but is a possible consequence of captopril use in salt/volume depleted persons (such as those treated vigorously with diuretics), patients with heart failure or those patients undergoing renal dialysis. (See PRECAUTIONS: Drug Interactions.) In heart failure, where the blood pressure was either normal or low, transient decreases in mean blood pressure >20% were recorded in about half of the patients. This transient hypotension is more likely to occur after any of the first several doses and is usually well tolerated, although rarely it has been associated with arrhythmia or conduction defects. A starting dose of 6.25 or 12.5 mg tid may minimize the hypotensive effect. Patients should be followed closely for the first 2 weeks of treatment and whenever the dose of captopril and/or diuretic is increased.

BECAUSE OF THE POTENTIAL FALL IN BLOOD PRESSURE IN THESE PATIENTS, THERAPY SHOULD BE STARTED UNDER VERY CLOSE MEDICAL SUPERVISION.

Fetal / Neonatal Morbidity and Mortality: ACE inhibitors can cause fetal and neonatal morbidity and death when administered to pregnant women. Several dozen cases have been reported in the world literature. When pregnancy is detected, ACE inhibitors should be discontinued as soon as possible.

The use of ACE inhibitors during the second and third trimesters of pregnancy has been associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death. Oligohydramnios has also been reported, presumably resulting from decreased fetal renal function; oligohydramnios in this setting has been associated with fetal limb contractures, craniofacial deformation, and hypoplastic lung development. Prematurity, intrauterine growth retardation, and patent ductus arteriosus have also been reported, although it is not clear whether these occurrences were due to the ACE-inhibitor exposure.

These adverse effects do not appear to have resulted from intrauterine ACE-inhibitor exposure that has been limited to the first trimester. Mothers whose embryos and fetuses are exposed to ACE inhibitors only during the first trimester should be so informed. Nonetheless, when patients become pregnant, physicians should make every effort to discontinue the use of captopril as soon as possible.

Rarely (probably less often than once in every thousand pregnancies), no alternative to ACE inhibitors will be found. In these rare cases, the mothers should be apprised of the potential hazards to their fetuses, and serial ultrasound examinations should be performed to assess the intraamniotic environment.

If oligohydramnios is observed, captopril should be discontinued unless it is considered life-saving for the mother. Contraction stress testing (CST), a non-stress test (NST), or biophysical profiling (BPP) may be appropriate, depending upon the week of pregnancy. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury.

Infants with histories of *in utero* exposure to ACE inhibitors should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion. Exchange transfusion or dialysis may be required as a means of reversing hypotension and/or substituting for disordered renal function. While captopril may be removed from the adult circulation by hemodialysis, there is inadequate data concerning the effectiveness of hemodialysis for removing it from the circulation of neonates or children. Peritoneal dialysis is not effective for removing captopril; there is no information concerning exchange transfusion for removing captopril from the general circulation.

When captopril was given to rabbits at doses about 0.8 to 70 times (on a mg/kg basis) the maximum recommended human dose, low incidences of craniofacial malformations were seen. No teratogenic effects of captopril were seen in studies of pregnant rats and hamsters. On a mg/kg basis, the doses used were up to 150 times (in hamsters) and 625 times (in rats) the maximum recommended human dose.

PRECAUTIONS: General: *Impaired Renal Function*—Hypertension–Some hypertensive patients with renal disease, particularly those with severe renal artery stenosis, have developed increases in BUN and serum creatinine. It may be necessary to reduce captopril dosage and/or discontinue diuretic. For some of these patients, normalization of blood pressure and maintenance of adequate renal perfusion may not be possible. Heart Failure—About 20% of patients develop stable elevations of BUN and serum creatinine >20% above normal or baseline upon long-term treatment. Less than 5% of patients, generally with severe preexisting renal disease, required discontinuation due to progressively increasing creatinine. (See DOSAGE AND ADMINISTRATION, ADVERSE REACTIONS: Altered Laboratory Findings.) *Hyperkalemia:* Elevations in serum potassium have been observed in some patients treated with ACE inhibitors, including captopril. When treated with ACE inhibitors, patients at risk for the development of hyperkalemia include those with: renal insufficiency; diabetes mellitus; and those using concomitant potassium-sparing diuretics, potassium supplements or potassium-containing salt substitutes; or other drugs associated with increases in serum potassium. (See PRECAUTIONS: Drug Interactions; ADVERSE REACTIONS: Altered Laboratory Findings.) *Cough*—Cough has been reported with the use of ACE inhibitors. Characteristically, the cough is nonproductive, persistent and resolves after discontinuation of therapy. ACE inhibitor-induced cough should be considered as part of the differential diagnosis of cough. *Valvular Stenosis*—A theoretical concern, for risk of decreased coronary perfusion, has been noted regarding vasodilator treatment in patients with aortic stenosis due to decreased afterload reduction. *Surgery/Anesthesia*—If hypotension occurs during surgery or anesthesia, and is considered due to the effects of captopril, it is correctable by volume expansion.

Pregnancy. Female patients of childbearing age should be told about the consequences of second and third-trimester exposure to ACE inhibitors, and they should also be told that these consequences do not appear to have resulted from intrauterine ACE-inhibitor exposure that has been limited to the first trimester. These patients should be asked to report pregnancies to their physicians as soon as possible.

Drug Interactions: *Hypotension–Patients on Diuretic Therapy*—Precipitous reduction of blood pressure may occasionally occur within the 1st hour after administration of the initial captopril dose in patients on diuretics, especially those recently placed on diuretics, and those on severe dietary salt restriction or dialysis. This possibility can be minimized by either discontinuing the diuretic or increasing the salt intake about 1 week prior to initiation of captopril therapy or by initiating therapy with small doses (6.25 or 12.5 mg). Alternatively, provide medical supervision for at least 1 hour after the initial dose.

Agents Having Vasodilator Activity—In heart failure patients, vasodilators should be administered with caution.

Agents Causing Renin Release—Captopril's effect will be augmented by antihypertensive agents that cause renin release.

Agents Affecting Sympathetic Activity—The sympathetic nervous system may be especially important in supporting blood pressure in patients receiving captopril alone or with diuretics. Beta-adrenergic blocking drugs add some further antihypertensive effect to captopril, but the overall response is less than additive. Therefore, use agents affecting sympathetic activity (e.g., ganglionic blocking agents or adrenergic neuron blocking agents) with caution.

Agents Increasing Serum Potassium—Give potassium-sparing diuretics or potassium supplements only for documented hypokalemia, and then with caution, since they may lead to a significant increase of serum potassium. Use potassium-containing salt substitutes with caution.

Inhibitors of Endogenous Prostaglandin Synthesis—Indomethacin and other nonsteroidal anti-inflammatory agents may reduce the antihypertensive effect of captopril, especially in low renin hypertension.

Lithium—Increased serum lithium levels and symptoms of lithium toxicity have been reported in patients receiving concomitant lithium and ACE inhibitor therapy. These drugs should be coadministered with caution and frequent monitoring of serum lithium levels is recommended. If a diuretic is also used, it may increase the risk of lithium toxicity.

Drug/Laboratory Test Interaction: Captopril may cause a false-positive urine test for acetone.

Carcinogenesis, Mutagenesis and Impairment of Fertility: Two-year studies with doses of 50 to 1350 mg/kg/day in mice and rats failed to show any evidence of carcinogenic potential. Studies in rats have revealed no impairment of fertility.

Pregnancy Categories C (first trimester) and D (second and third trimesters)
See WARNINGS: Fetal/Neonatal Morbidity and Mortality.

Nursing Mothers: Concentrations of captopril in human milk are approximately one percent of those in maternal blood. Because of the potential for serious adverse reactions in nursing infants from captopril, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of CAPOTEN to the mother. (See PRECAUTIONS: Pediatric Use.)

Pediatric Use: Safety and effectiveness in children have not been established. There is limited experience reported in the literature with the use of captopril in the pediatric population; dosage on a weight basis, was generally reported to be comparable to or less than that used in adults.

Infants, especially newborns, may be more susceptible to the adverse hemodynamic effects of captopril. Excessive, prolonged and unpredictable decreases in blood pressure and associated complications, including oliguria and seizures, have been reported.

CAPOTEN (captopril) should be used in children only if other measures for controlling blood pressure have not been effective.

ADVERSE REACTIONS: Reported incidences are based on clinical trials involving approximately 7000 patients.

Renal: About 1 of 100 patients developed proteinuria (see WARNINGS). Renal insufficiency, renal failure, nephrotic syndrome, polyuria, oliguria, and urinary frequency in 1 to 2 of 1000 patients.

Hematologic: Neutropenia/agranulocytosis has occurred (see WARNINGS). Anemia, thrombocytopenia, and pancytopenia have been reported.

Dermatologic: Rash, (usually maculopapular, rarely urticarial), often with pruritus, and sometimes with fever and eosinophilia, in about 4 to 7 of 100 patients (depending on renal status and dose), usually during the 1st 4 weeks of therapy. Pruritus, without rash, in about 2 of 100 patients. A reversible associated pemphigoid-like lesion, and photosensitivity, have also been reported. Flushing or pallor in 2 to 5 of 1000 patients.

Cardiovascular: Hypotension may occur; see WARNINGS and PRECAUTIONS [Drug Interactions] for discussion of hypotension with captopril therapy. Tachycardia, chest pain, and palpitations each in about 1 of 100 patients. Angina pectoris, myocardial infarction, Raynaud's syndrome, and congestive heart failure each in 2 to 3 of 1000 patients.

Dysgeusia: Approximately 2 to 4 (depending on renal status and dose) of 100 patients developed a diminution or loss of taste perception; taste impairment is reversible and usually self-limited even with continued drug use (2 to 3 months).

Angioedema: Angioedema involving the extremities, face, lips, mucous membranes, tongue, glottis or larynx has been reported in approximately one in 1000 patients. Angioedema involving the upper airways has caused fatal airway obstruction. (See WARNINGS.)

Cough: Cough has been reported in 0.5-2% of patients treated with captopril in clinical trials (see PRECAUTIONS: General: *Cough*).

The following have been reported in about 0.5 to 2 percent of patients but did not appear at increased frequency compared to placebo or other treatments used in controlled trials: gastric irritation, abdominal pain, nausea, vomiting, diarrhea, anorexia, constipation, aphthous ulcers, peptic ulcer, dizziness, headache, malaise, fatigue, insomnia, dry mouth, dyspnea, cough, alopecia, paresthesias.

Other clinical adverse effects reported since the drug was marketed are listed below by body system. In this setting, an incidence or causal relationship cannot be accurately determined.

General: Asthenia, gynecomastia.
Cardiovascular: Cardiac arrest, cerebrovascular accident/insufficiency, rhythm disturbances, orthostatic hypotension, syncope.
Dermatologic: Bullous pemphigus, erythema multiforme (including Stevens-Johnson syndrome), exfoliative dermatitis.
Gastrointestinal: Pancreatitis, glossitis, dyspepsia.
Hematologic: Anemia, including aplastic and hemolytic.
Hepatobiliary: Jaundice, hepatitis, including rare cases of necrosis, cholestasis.
Metabolic: Symptomatic hyponatremia.
Musculoskeletal: Myalgia, myasthenia.
Nervous/Psychiatric: Ataxia, confusion, depression, nervousness, somnolence.
Respiratory: Bronchospasm, eosinophilic pneumonitis, rhinitis.
Special Senses: Blurred vision.
Urogenital: Impotence.

As with other ACE inhibitors, a syndrome has been reported which may include: fever, myalgia, arthralgia, interstitial nephritis, vasculitis, rash or other dermatologic manifestations, eosinophilia and an elevated ESR.

Fetal/Neonatal Morbidity and Mortality
See WARNINGS: Fetal/Neonatal Morbidity and Mortality.

Altered Laboratory Findings: *Serum Electrolytes:* Hyperkalemia: small increases in serum potassium, especially in patients with renal impairment (see PRECAUTIONS).

Hyponatremia: particularly in patients receiving a low sodium diet or concomitant diuretics.

BUN/Serum Creatinine: Transient elevations of BUN or serum creatinine especially in volume or salt depleted patients or those with renovascular hypertension may occur. Rapid reduction of long-standing or markedly elevated blood pressure can result in decreases in the glomerular filtration rate and, in turn, lead to increases in BUN or serum creatinine.

Hematologic: A positive ANA has been reported.

Liver Function Tests: Elevations of liver transaminases, alkaline phosphatase, and serum bilirubin have occurred.

OVERDOSAGE: Primary concern is correction of hypotension. Volume expansion with an I.V. infusion of normal saline is the treatment of choice for restoration of blood pressure.

While captopril may be removed from the adult circulation by hemodialysis, there is inadequate data concerning the effectiveness of hemodialysis for removing it from the circulation of neonates or children. Peritoneal dialysis is not effective for removing captopril; there is no information concerning exchange transfusion for removing captopril from the general circulation.

DOSAGE AND ADMINISTRATION: CAPOTEN (captopril) should be taken one hour before meals. In hypertension, CAPOTEN may be dosed bid or tid. Dosage must be individualized; see DOSAGE AND ADMINISTRATION section of package insert for detailed information regarding dosage in hypertension and in heart failure. Because CAPOTEN (captopril) is excreted primarily by the kidneys, dosage adjustments are recommended for patients with impaired renal function.

Consult package insert before prescribing CAPOTEN (captopril).

HOW SUPPLIED: Available in tablets of: 12.5 mg in bottles of 100 and 1000; 25 mg in bottles of 100 and 1000; 50 mg in bottles of 100 and 1000; 100 mg of bottles of 100; and in UNIMATIC® unit-dose packs of 100 tablets. (J3-658Z)

References: 1. Physicians' Desk Reference®, 45th ed, Oradell, NJ. Medical Economics Co Inc, 1991, pp 2141-2143. **2.** Captopril Multicenter Research Group: A placebo-controlled trial of captopril in refractory chronic congestive heart failure. *JACC* 2:755-763, 1983. **3.** The Captopril-Digoxin Multicenter Research Group: Comparative effects of therapy with captopril and digoxin in patients with mild to moderate heart failure. *JAMA* 259:539-544, 1988.

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0522-517

Issued: May 1992

impaired LV compliance. However, the relation between such regions of myocardial cell disarray and the magnitude of wall thickness in the same areas of the left ventricle has not been defined. In the present study, no correlation was identified between LV wall thickness and the amount of myocardium disorganized in the same tissue section, either when calculated separately for the ventricular septum, and anterolateral and posterior free walls, or when expressed for all 3 regions combined. Therefore, in patients with hypertrophic cardiomyopathy: (1) disorganized myocardial architecture is not confined to greatly thickened portions of the LV wall, but regions of the left ventricle with normal or mildly increased thickness may also be disordered; and (2) whereas both LV wall thickening and cellular disorganization are manifestations of the primary cardiomyopathic process, these 2 morphologic features do not appear to be related with regard to their extent and distribution within the LV wall.

METHODS

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Effect of an Anterior Wall Motion Abnormality on the Results of Single-Plane and Biplane Left Ventriculography

David A. Tate, David Weaver, and Gregory J. Dehmer

Although the biplane area-length method would be optimal for all left ventriculograms, many catheterization laboratories only have single-plane imaging equipment. In such laboratories, biplane determinations can still be obtained, but a second contrast injection is needed. A retrospective analysis of 91 consecutive biplane ventriculograms was performed to define practical guidelines for predicting when the ejection fraction calculated by the biplane method would differ significantly from the single-plane value. These guidelines were derived from information that would immediately be available to the operator in the laboratory at the time of the procedure. By multivariate analysis, the only predictor of a higher ejection fraction calculated by the biplane method was the presence of an anterior wall motion abnormality. This observation was tested prospectively in 60 additional patients. In these patients, the biplane ejection fraction exceeded the single-plane value by 0.05 ± 0.04 in those with anterior wall motion abnormalities compared with by -0.01 ± 0.04 in those without abnormalities. Thus, in cases where only single-plane imaging equipment is available, the data define a practical way to determine if a separate contrast injection in the left anterior oblique view would likely result in a higher value for the ejection fraction calculated by the biplane method.

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An Improved Method for Adjusting the QT Interval for Heart Rate (the Framingham Heart Study)

Alex Sagie, Martin G. Larson, Robert J. Goldberg, James R. Bengtson, and Daniel Levy

To evaluate the heart rate QT association the QT interval was measured on the initial electrocardiogram of 5,018 Framingham Heart Study subjects. A linear regression model was developed for correcting QT according to RR cycle length, and comparison with Bazett's correction $QT/\sqrt{RR}$ was made. The linear model yielded the following: $QT_{LC} =$

QT + 0.154(1 − RR). The linear equation corrects QT more reliably than the Bazett's formula that overcorrects QT at fast heart rates and undercorrects it at slow heart rates. The linear correction is more accurate and convenient than Bazett's correction, and alleviates the need to apply secondary correction in clinical practice.

CARDIOVASCULAR PHARMACOLOGY

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Reversal of Human Platelet Aggregation by Low Concentrations of Nitroglycerin In Vitro in Normal Subjects
Yuliy Y. Chirkov, Jurate I. Naujalis, Sylvia Barber, R. Edward Sage, David W. Gove, John K. Brealey, and John D. Horowitz

Previous in vitro studies have failed to reveal any antiplatelet effects of nitroglycerin except in very high concentrations. The current investigation examined the possible action of nitroglycerin in reversing platelet aggregation induced by adenosine diphosphate. Nitroglycerin-induced reversal of platelet aggregation, as assessed by optical aggregometry, was concentration-dependent. Significant effects occurred with concentrations 10^{-8} M and higher. The concentration of nitroglycerin associated with 50% reversal of aggregation was $1.52 \pm 0.24 \times 10^{-6}$ M. Electron microscopy confirmed that 1 μM of nitroglycerin was sufficient to induce marked limitation of both platelet aggregation and associated morphologic changes. The results of the current study suggest a pivotal role of nitroglycerin in restoring homeostatic mechanisms in the face of incipient platelet aggregation.

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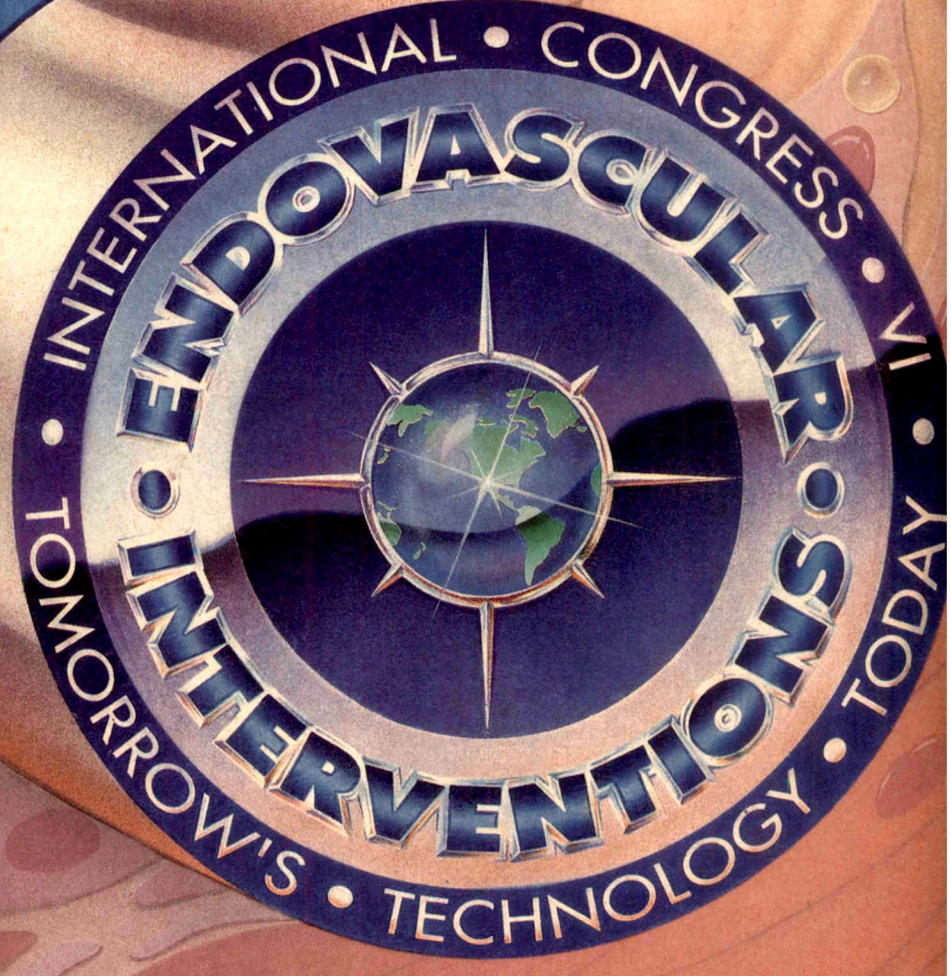
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Cardiac Transplant Recipients Are Sex Blind to Their Heart Donors
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Program Directors: Edward B. Diethrich, MD, and Richard R. Heuser, MD

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A NEW TIMESAVING SOLUTION

Activase® (Alteplase) 100 mg vial for added timesaving convenience in the emergency or critical care setting

Rapidly reconstituted

- New 100 mg vial package contains Activase® lyophilized powder, double-sided, sterile, siliconized transfer device, and diluent – all the necessary components in one convenient package
- Utilization of the new, single-vial design and transfer device can reduce the time necessary to reconstitute Activase® by two-thirds[1]

Conveniently administered – can eliminate the need for an IV bag

- Specially designed vial with plastic hanger so vial can be hung for direct infusion



- 100 mg vial must be used with vented IV tubing or vented adapter spike and non-vented IV tubing
- Contents can be transferred to an IV bag if preferred

20 mg and/or 50 mg vials plus new 100 mg vial provide dosing alternatives

- 20 mg and 50 mg vials for accurate dosing in acute myocardial infarction (AMI) for patients <65 kg
- New 100 mg vial permits convenient dosing for patients ≥65 kg with AMI or acute massive pulmonary embolism

Please see brief summary of prescribing information for Activase® on following page.

1. Data on file, Genentech, Inc.

ACTIVASE
ALTEPLASE, RECOMBINANT
A TISSUE PLASMINOGEN ACTIVATOR

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ACTIVASE® (Alteplase)

Brief Summary

Consult full prescribing information before using.

INDICATIONS AND USAGE: Acute Myocardial Infarction: Activase® is indicated for use in the management of acute myocardial infarction (AMI) in adults for the lysis of thrombi obstructing coronary arteries, the reduction of infarct size, the improvement of ventricular function following AMI, the reduction of the incidence of congestive heart failure and the reduction of mortality associated with AMI. Treatment should be initiated as soon as possible after the onset of AMI symptoms (see CLINICAL PHARMACOLOGY section of full prescribing information).

Pulmonary Embolism: Activase® is indicated in the management of acute massive pulmonary embolism (PE) in adults:

for the lysis of acute pulmonary emboli, defined as obstruction of blood flow to a lobe or multiple segments of the lungs, and

for the lysis of pulmonary emboli accompanied by unstable hemodynamics, e.g., failure to maintain blood pressure without supportive measures.

The diagnosis should be confirmed by objective means, such as pulmonary angiography or noninvasive procedures such as lung scanning.

CONTRAINDICATIONS: Because thrombolytic therapy increases the risk of bleeding, Activase® is contraindicated in the following situations: • Active internal bleeding • History of cerebrovascular accident • Recent (within two months) intracranial or intraspinal, surgery or trauma (see WARNINGS) • Intracranial neoplasm, arteriovenous malformation, or aneurysm • Known bleeding diathesis • Severe uncontrolled hypertension

WARNINGS: Bleeding: The most common complication encountered during Activase® therapy is bleeding. The type of bleeding associated with thrombolytic therapy can be divided into two broad categories: • Internal bleeding, involving the gastrointestinal tract, genitourinary tract, retroperitoneal or intracranial sites. • Superficial or surface bleeding, observed mainly at invaded or disturbed sites (e.g., venous cutdowns, arterial punctures, sites of recent surgical intervention).

The concomitant use of heparin anticoagulation may contribute to bleeding. Some of the hemorrhagic episodes occurred one or more days after the effects of Activase® had dissipated, but while heparin therapy was continuing.

As fibrin is lysed during Activase® therapy, bleeding from recent puncture sites may occur. Therefore, thrombolytic therapy requires careful attention to all potential bleeding sites (including catheter insertion sites, arterial and venous puncture sites, cutdown sites and needle puncture sites).

Intramuscular injections and nonessential handling of the patient should be avoided during treatment with Activase®. Venipunctures should be performed carefully and only as required.

Should an arterial puncture be necessary during an infusion of Activase®, it is preferable to use an upper extremity vessel that is accessible to manual compression. Pressure should be applied for at least 30 minutes, a pressure dressing applied and the puncture site checked frequently for evidence of bleeding.

Should serious bleeding (not controllable by local pressure) occur, the infusion of Activase® and any concomitant heparin should be terminated immediately.

Each patient being considered for therapy with Activase® should be carefully evaluated and anticipated benefits weighed against potential risks associated with therapy.

In the following conditions, the risks of Activase® therapy may be increased and should be weighed against the anticipated benefits: • Recent (within 10 days) major surgery, e.g., coronary artery bypass graft, obstetrical delivery, organ biopsy, previous puncture of noncompressible vessels • Cerebrovascular disease • Recent gastrointestinal or genitourinary bleeding (within 10 days) • Recent trauma (within 10 days) • Hypertension: systolic BP ≥ 180 mm Hg and/or diastolic BP ≥ 110 mm Hg • High likelihood of left heart thrombus, e.g., mitral stenosis with atrial fibrillation • Acute pericarditis • Subacute bacterial endocarditis • Hemostatic defects including those secondary to severe hepatic or renal disease • Significant liver dysfunction • Pregnancy • Diabetic hemorrhagic retinopathy, or other hemorrhagic ophthalmic conditions • Septic thrombophlebitis or occluded AV cannula at seriously infected site • Advanced age, i.e., over 75 years old • Patients currently receiving oral anticoagulants, e.g., warfarin sodium • Any other condition in which bleeding constitutes a significant hazard or would be particularly difficult to manage because of its location

Arrhythmias: Coronary thrombolysis may result in arrhythmias associated with reperfusion. These arrhythmias (such as sinus bradycardia, accelerated idioventricular rhythm, ventricular premature depolarizations, ventricular tachycardia) are not different from those often seen in the ordinary course of acute myocardial infarction and may be managed with standard antiarrhythmic measures. It is recommended that antiarrhythmic therapy for bradycardia and/or ventricular irritability be available when infusions of Activase®, Alteplase, are administered.

Pulmonary Embolism: It should be recognized that the treatment of pulmonary embolism with Activase®, Alteplase, has not been shown to constitute adequate clinical treatment of underlying deep vein thrombosis. Furthermore, the possible risk of reembolization due to the lysis of underlying deep venous thrombi should be considered.

PRECAUTIONS: General: Standard management of myocardial infarction or pulmonary embolism should be implemented concomitantly with Activase® treatment. Noncompressible arterial puncture must be avoided (i.e., internal jugular and subclavian punctures should be avoided to minimize bleeding from noncompressible sites). Arterial and venous punctures should be minimized. In the event of serious bleeding, Activase® and heparin should be discontinued immediately. Heparin effects can be reversed by protamine.

Readministration: There is no experience with readministration of Activase®. If an anaphylactoid reaction occurs, the infusion should be discontinued immediately and appropriate therapy initiated.

Although sustained antibody formation in patients receiving one dose of Activase® has not been documented, readministration should be undertaken with caution. Detectable levels of antibody (a single point measurement) were reported in one patient but subsequent antibody test results were negative.

Laboratory Tests: During Activase® therapy, if coagulation tests and/or measures of fibrinolytic activity are performed, the results may be unreliable unless specific precautions are taken to prevent *in vitro* artifacts. Activase® is an enzyme that when present in blood in pharmacologic concentrations remains active under *in vitro* conditions. This can lead to degradation of fibrinogen in blood samples removed for analysis. Collection of blood samples in the presence of aprotinin (150-200 units/mL) can to some extent mitigate this phenomenon.

Drug Interactions: The interaction of Activase® with other cardioactive drugs has not been studied. In addition to bleeding associated with heparin and vitamin K antagonists, drugs that alter platelet function (such as acetylsalicylic acid, dipyridamole) may increase the risk of bleeding if administered prior to, during or after Activase® therapy.

Use of Anticoagulants: Heparin has been administered concomitantly with and following infusions of Activase® to reduce the risk of rethrombosis. Because either heparin or Activase® alone may cause bleeding complications, careful monitoring for bleeding is advised, especially at arterial puncture sites.

Pregnancy (Category C): Animal reproduction studies have not been conducted with Activase®. It is also not known whether Activase® can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Activase® should be given to a pregnant woman only if clearly needed.

Pediatric Use: Safety and effectiveness of Activase® in children has not been established.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies in animals have not been performed to evaluate the carcinogenic potential or the effect on fertility. Short-term studies, which evaluated tumorigenicity of Activase® and effect on tumor metastases in rodents, were negative.

Studies to determine mutagenicity (Ames test) and chromosomal aberration assays in human lymphocytes were negative at all concentrations tested. Cytotoxicity, as reflected by a decrease in mitotic index, was evidenced only after prolonged exposure and only at the highest concentrations tested.

Nursing Mothers: It is not known whether Activase® is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Activase®, Alteplase, is administered to a nursing woman.

ADVERSE REACTIONS: Bleeding: The most frequent adverse reaction associated with Activase® is bleeding. The type of bleeding associated with thrombolytic therapy can be divided into two broad categories: • Internal bleeding, involving the gastrointestinal tract, genitourinary tract, retroperitoneal or intracranial sites. • Superficial or surface bleeding, observed mainly at invaded or disturbed sites (e.g., venous cutdowns, arterial punctures, sites of recent surgical intervention).

The following incidence of significant internal bleeding (estimated as >250 cc blood loss) has been reported in studies in over 800 patients treated at all doses:

	Total Dose ≤ 100 mg	Total Dose > 100 mg
gastrointestinal	5%	5%
genitourinary	4%	4%
ecchymosis	1%	<1%
retroperitoneal	<1%	<1%
epistaxis	<1%	<1%
gingival	<1%	<1%

The incidence of intracranial bleeding (ICB) in patients treated with Activase® is as follows:

Dose	Number of Patients	%
100 mg	3272	0.4
150 mg	1779	1.3
1-1.4 mg/kg	237	0.4

These data indicate that a dose of 150 mg of Activase® should not be used because it has been associated with an increase in intracranial bleeding.

Recent data indicate that the incidence of stroke in 6 randomized double-blind placebo controlled trials[1-7] is not significantly different in the Activase® treated patients compared to those treated with placebo (37/3161, 1.2% versus 27/3092, 0.9%, respectively)(p = 0.26).

Should serious bleeding in a critical location (intracranial, gastrointestinal, retroperitoneal, pericardial) occur, Activase® therapy should be discontinued immediately, along with any concomitant therapy with heparin.

ACTIVASE® (Alteplase)

Fibrin which is part of the hemostatic plug formed at needle puncture sites will be lysed during Activase® therapy. Therefore, Activase® therapy requires careful attention to potential bleeding sites, e.g., catheter insertion sites, arterial puncture sites.

Allergic Reactions: No serious or life-threatening allergic reactions have been reported. Other mild hypersensitivity reactions such as urticaria have been observed occasionally.

Other Adverse Reactions: Other adverse reactions have been reported, principally nausea and/or vomiting, hypotension, and fever. These reactions are frequent sequelae of myocardial infarction and may or may not be attributable to Activase® therapy.

DOSAGE AND ADMINISTRATION: Activase® is for intravenous administration only.

Acute Myocardial Infarction: Administer Activase® as soon as possible after the onset of symptoms.

The recommended dose is 100 mg administered as 60 mg (34.8 million IU) in the first hour (of which 6 to 10 mg is administered as a bolus over the first 1-2 minutes), 20 mg (11.6 million IU) over the second hour, and 20 mg (11.6 million IU) over the third hour. For smaller patients (less than 65 kg), a dose of 1.25 mg/kg administered over 3 hours, as described above, may be used.[8]

a. The bolus dose may be prepared in one of the following ways:
   1. By removing 6 to 10 mL from the vial of reconstituted (1 mg/mL) Activase® using a syringe and needle. If this method is used with the 20 mg or 50 mg vials, the syringe should not be primed with air and the needle should be inserted into the Activase® vial stopper. If the 100 mg vial is used, the needle should be inserted away from the puncture mark made by the transfer device.
   2. By removing 6 to 10 mL from a port (second injection site) on the infusion line after the infusion set is primed.
   3. By programming an infusion pump to deliver a 6 to 10 mL (1 mg/mL) bolus at the initiation of the infusion.

b. The remainder of the Activase® dose may be administered as follows:

20 mg, 50 mg vials, administer using either a polyvinyl chloride bag or glass vial and infusion set.

100 mg vials, insert the spike end of an infusion set through the same puncture site created by the transfer device in the stopper of the vial of reconstituted Activase®. Hang the Activase® vial from the plastic molded capping attached to the bottom of the vial.

Although the use of anticoagulants and antiplatelet drugs during and following administration of Activase® has not been shown to be of unequivocal benefit, heparin has been administered concomitantly for 24 hours or longer in more than 90% of patients. Aspirin and/or dipyridamole have been given either during and/or following heparin treatment.

Pulmonary Embolism: The recommended dose is 100 mg administered by intravenous infusion over two hours. Heparin therapy should be instituted or reinstituted near the end of or immediately following the Activase® infusion when the partial thromboplastin time or thrombin time returns to twice normal or less.

The dose may be administered using the instructions described above in Acute Myocardial Infarction (b).

A DOSE OF 150 MG OF ACTIVASE®, ALTEPLASE, SHOULD NOT BE USED BECAUSE IT HAS BEEN ASSOCIATED WITH AN INCREASE IN INTRACRANIAL BLEEDING.

Reconstitution and Dilution: Activase® should be reconstituted by aseptically adding the appropriate volume of the accompanying Sterile Water for Injection, USP to the vial. It is important that Activase® be reconstituted only with Sterile Water for Injection, USP, without preservatives. Do not use Bacteriostatic Water for Injection, USP. The reconstituted preparation results in a colorless to pale yellow transparent solution containing Activase® 1 mg/mL at approximately pH 7.3. The osmolality of this solution is approximately 215 mOsm/kg.

Because Activase® contains no antibacterial preservatives, it should be reconstituted immediately before use. The solution may be used for intravenous administration within 8 hours following reconstitution when stored between 2-30°C (36-86°F). Before further dilution or administration, the product should be visually inspected for particulate matter and discoloration prior to administration whenever solution and container permit.

Activase® may be administered as reconstituted at 1 mg/mL. As an alternative, the reconstituted solution may be diluted further immediately before administration in an equal volume of 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP to yield a concentration of 0.5 mg/mL. Either polyvinyl chloride bags or glass vials are acceptable. Activase® is stable for up to 8 hours in these solutions at room temperature. Exposure to light has no effect on the stability of these solutions. Excessive agitation during dilution should be avoided; mixing should be accomplished with gentle swirling and/or slow inversion. Do not use other infusion solutions, e.g., Sterile Water for Injection, USP or preservative-containing solutions for further dilution.

20 mg and 50 mg vials: Reconstitution should be carried out using a large bore needle (e.g., 18 gauge) and a syringe, directing the stream of Sterile Water for Injection, USP into the lyophilized cake. **DO NOT USE IF VACUUM IS NOT PRESENT.** Slight foaming upon reconstitution is not unusual; standing undisturbed for several minutes is usually sufficient to allow dissipation of any large bubbles.

No other medication should be added to infusion solutions containing Activase®, Alteplase. Any unused infusion solution should be discarded.

100 mg vials: Reconstitution should be carried out using the transfer device provided, adding the contents of the accompanying 100 mL vial of Sterile Water for Injection, USP to the contents of the 100 mg vial of Activase® powder. Slight foaming upon reconstitution is not unusual; standing undisturbed for several minutes is usually sufficient to allow dissipation of any large bubbles. Please refer to the accompanying Instructions for Reconstitution and Administration. **100 MG VIALS DO NOT CONTAIN VACUUM.**

100 MG VIAL RECONSTITUTION

1. Use aseptic technique throughout.
2. Remove the protective flip-caps from one vial of Activase® and one vial of Sterile Water for Injection, USP (SWFI).
3. Open the package containing the transfer device by peeling the paper label off the package.
4. Remove the protective cap from one end of the transfer device and keeping the vial of SWFI upright, insert the piercing pin vertically into the center of the stopper of the vial of SWFI.
5. Remove the protective cap from the other end of the transfer device. **DO NOT INVERT THE VIAL OF SWFI.**
6. Holding the vial of Activase® upside-down, position it so that the center of the stopper is directly over the exposed piercing pin of the transfer device.
7. Push the vial of Activase® down so that the piercing pin is inserted through the center of the Activase® vial stopper.
8. Invert the two vials so that the vial of Activase® is on the bottom (upright) and the vial of SWFI is upside-down, allowing the SWFI to flow down through the transfer device. Allow the entire contents of the vial of SWFI to flow into the Activase® vial (approximately 0.5 cc of SWFI will remain in the diluent vial). Approximately two minutes are required for this procedure.
9. Remove the transfer device and the empty SWFI vial from the Activase® vial. Safely discard both the transfer device and the empty diluent vial according to institutional procedures.
10. Swirl gently to dissolve the Activase® powder. **DO NOT SHAKE.**

No other medication should be added to infusion solutions containing Activase®, Alteplase. Any unused infusion solution should be discarded.

HOW SUPPLIED: Activase® is supplied as a sterile, lyophilized powder in 20 mg and 50 mg vials containing vacuum and in 100 mg vials without vacuum.

Each 20 mg Activase® vial (11.6 million IU) is packaged with diluent for reconstitution (20 mL Sterile Water for Injection, USP): NDC 50242-044-12.

Each 50 mg Activase® vial (29.0 million IU) is packaged with diluent for reconstitution (50 mL Sterile Water for Injection, USP): NDC 50242-044-13.

Each 100 mg Activase® vial (58 million IU) is packaged with diluent for reconstitution (100 mL Sterile Water for Injection, USP), and one transfer device: NDC 50242-085-27.

Storage: Store lyophilized Activase® at controlled room temperature not to exceed 30°C (86°F), or under refrigeration (2-8°C/36-46°F). Protect the lyophilized material during extended storage from excessive exposure to light.

Do not use beyond the expiration date stamped on the vial.

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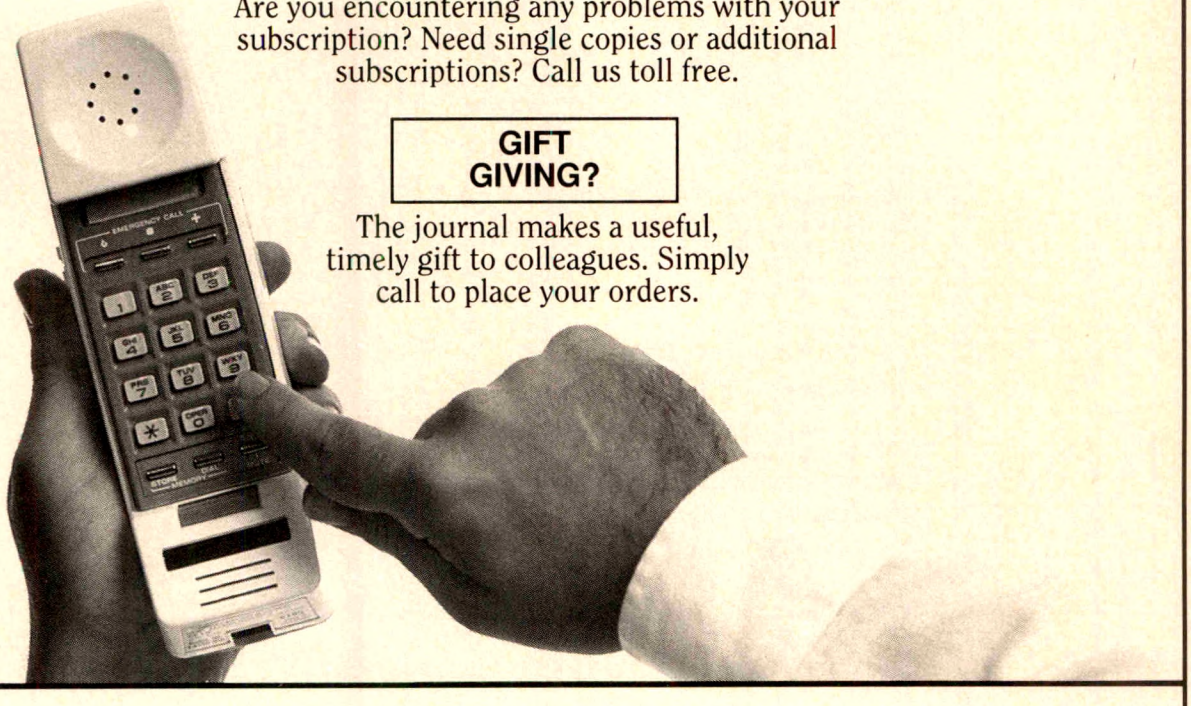
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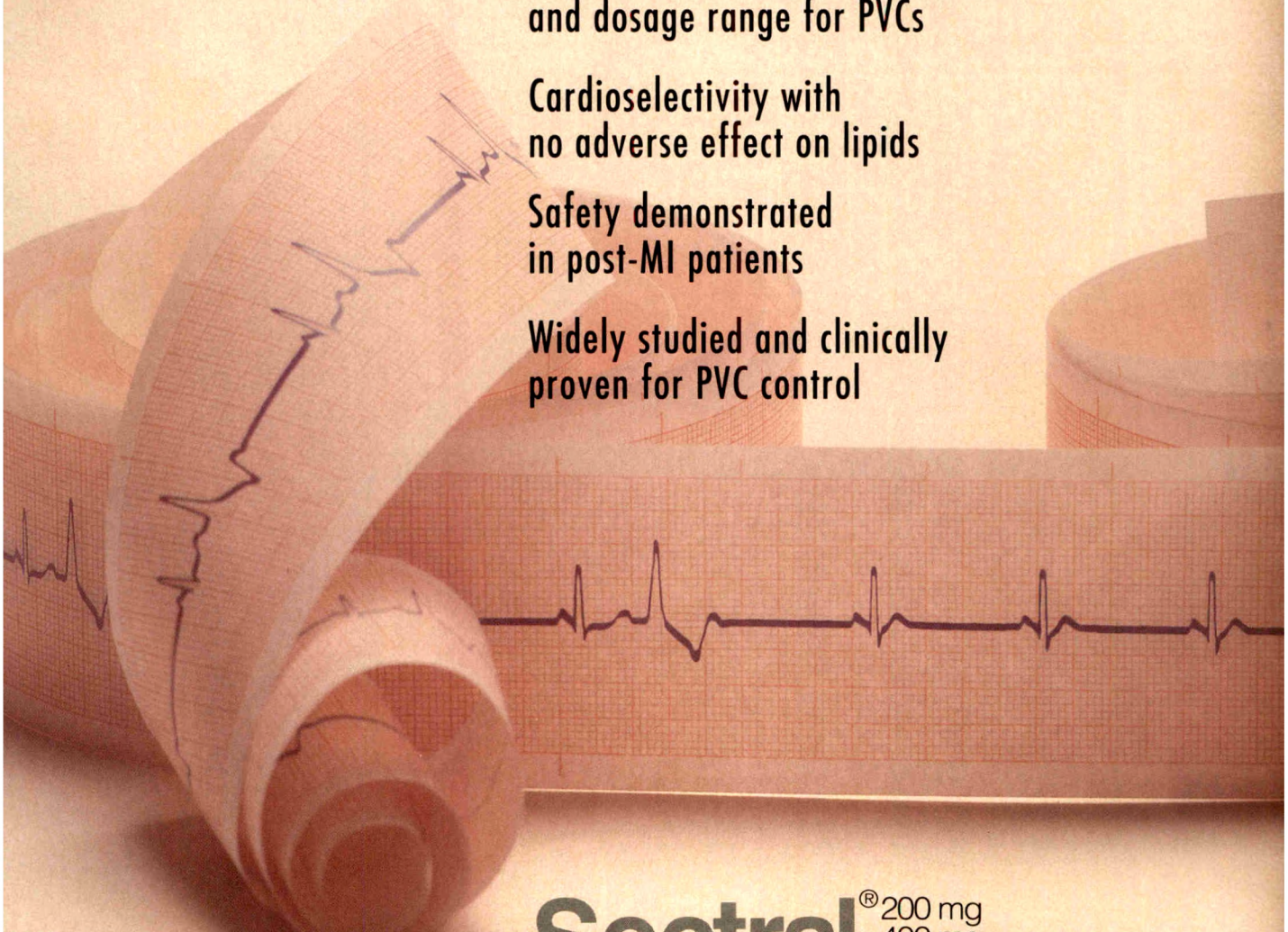
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THE CARDIOSELECTIVE BETA BLOCKER FOR PVC CONTROL

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Sectral® 200 mg 400 mg CAPSULES
acebutolol HCl

THE CARDIOSELECTIVE BETA BLOCKER FOR PVC CONTROL

Usual starting dose	**200 mg b.i.d.**
Optimal PVC response	**600 mg to 1200 mg per day**
Use in elderly	**Doses above 800 mg per day should be avoided**

(Brief Summary. See Package Circular for full prescribing information.)

CONTRAINDICATIONS: SECTRAL is contraindicated in: 1) persistently severe bradycardia; 2) second- and third-degree heart block; 3) overt cardiac failure; 4) cardiogenic shock. (See WARNINGS)

WARNINGS: Cardiac Failure: Sympathetic stimulation may be essential for support of circulation in patients with diminished myocardial contractility and inhibition by β-adrenergic receptor blockade may precipitate more severe failure. Although β-blockers should be avoided in overt cardiac failure, SECTRAL can be used cautiously when heart failure is controlled with digitalis and/or diuretics. Digitalis and SECTRAL impair AV conduction. Withdraw SECTRAL if cardiac failure persists.

In Patients Without a History of Cardiac Failure: In patients with aortic or mitral valve disease or compromised left ventricular function, continued depression of the myocardium with β-blockers over time may lead to cardiac failure. Digitalize patients at first signs of failure, and/or give a diuretic and observe closely. Withdraw SECTRAL if cardiac failure persists.

Exacerbation of Ischemic Heart Disease Following Abrupt Withdrawal: Abrupt discontinuation of some β-blockers in coronary artery disease patients may exacerbate angina; in some cases, myocardial infarction and death have been reported. Caution such patients against interruption of therapy without a physician's advice. Even in the absence of overt ischemic heart disease, withdraw SECTRAL gradually over a period of about two weeks; observe carefully and advise patients to minimize physical activity during this time. (If desired, patients may be transferred directly to comparable doses of an alternative β-blocker without interruption of β-blocking therapy.) If exacerbation of angina occurs, restart full-dose anti-anginal therapy immediately and hospitalize patient until stabilized.

Peripheral Vascular Disease: β-antagonists reduce cardiac output and can precipitate/aggravate arterial insufficiency in patients with peripheral or mesenteric vascular disease. Exercise caution and observe such patients closely for progression of arterial obstruction.

Bronchospastic Diseases: Patients with Bronchospastic Disease Should, in General, Not Receive a β-Blocker. Because of its relative β_1-selectivity, low doses of SECTRAL may be used cautiously in such patients who do not respond to, or cannot tolerate, alternative treatment. Since β_1-selectivity is not absolute and is dose-dependent, use lowest possible dose of SECTRAL initially, preferably in divided doses. Make bronchodilator, e.g., theophylline, or a β_2-stimulant, available in advance with instructions for use.

Anesthesia and Major Surgery: The necessity/desirability of withdrawing β-blockers prior to major surgery is controversial; the heart's impaired ability to respond to β-adrenergically mediated reflex stimuli may enhance the risk of excessive myocardial depression during general anesthesia. Difficulty in restarting and maintaining the heartbeat also has been reported with beta-blockers. If treatment is continued, take special care when using anesthetics that depress the myocardium; use lowest possible SECTRAL dose. SECTRAL, like other β-blockers, is a competitive inhibitor of β-receptor agonists, so its effects can be reversed by cautious administration of such agents (e.g., dobutamine or isoproterenol). Symptoms of excessive vagal tone (e.g., profound bradycardia, hypotension) may be corrected with atropine.

Diabetes and Hypoglycemia: β-blockers may potentiate insulin-induced hypoglycemia and mask some symptoms such as tachycardia; dizziness and sweating are usually not significantly affected. Warn diabetics of possible masked hypoglycemia.

Thyrotoxicosis: β-adrenergic blockade may mask some clinical signs (tachycardia) of hyperthyroidism. Abrupt withdrawal of SECTRAL may precipitate a thyroid storm in patients suspected of developing thyrotoxicosis.

PRECAUTIONS: Impaired Renal or Hepatic Function: While there are no U.S. studies, foreign published experience shows that acebutolol has been used successfully in chronic renal insufficiency. Acebutolol is excreted via the G.I. tract, but the active metabolite, diacetolol, is eliminated mainly by the kidney. A linear relationship exists between renal clearance of diacetolol and creatinine clearance (Cl_{cr}); reduce daily dose of acebutolol by 50% when Cl_{cr} is less than 50 mL/min and by 75% when it is less than 25 mL/min. Use cautiously in patients with impaired hepatic function.

SECTRAL has been used successfully and without problems in elderly patients in U.S. clinical trials without specific dosage adjustment. However, in the elderly, lower maintenance doses may be required because bioavailability of SECTRAL and its metabolite are approximately doubled.

Information for Patients: Warn patients, especially those with evidence of coronary artery disease, against interruption or discontinuation of SECTRAL without physician supervision. Although cardiac failure rarely occurs in properly selected patients, advise patients to consult a physician if signs or symptoms suggestive of impending CHF, or unexplained respiratory symptoms, develop.

Warn patients of possible severe hypertensive reactions from concomitant use of α-adrenergic stimulants, e.g., nasal decongestants used in OTC cold medicines and nasal drops.

Clinical Laboratory Findings: SECTRAL, like other β-blockers has been associated with development of antinuclear antibodies (ANA). In prospective clinical trials, patients receiving SECTRAL had a dose-dependent increase in the development of positive ANA titers. Symptoms related to this laboratory abnormality were infrequent. Symptoms and ANA titers were reversible upon discontinuation of SECTRAL.

Drug Interactions: Catecholamine-depleting drugs may have additive effects when given with β-blockers. Observe patients treated with both agents closely for evidence of marked bradycardia or hypotension which may present as vertigo, syncope/presyncope, or orthostatic changes in blood pressure without compensatory tachycardia. Exaggerated hypertensive responses have been reported from use of β-adrenergic antagonists with α-adrenergic stimulants, including those in OTC cold remedies and vasoconstrictive nasal drops. Nonsteroidal anti-inflammatory drugs may blunt antihypertensive effects of beta-blockers.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Chronic oral toxicity studies in rats and mice, at doses 15 times the maximum recommended (60 kg) human dose, did not indicate carcinogenic potential for SECTRAL. Diacetolol, the major metabolite in man, was without carcinogenic potential in rats at doses up to 1800 mg/kg/d. SECTRAL and diacetolol also had no mutagenic potential in the Ames Test. No significant impact on reproductive performance or fertility was found in rats following SECTRAL or diacetolol doses of up to 240 or 1000 mg/kg/d, respectively.

Pregnancy: *Teratogenic Effects:* Pregnancy Category B: No teratogenic effects were seen in rat or rabbit reproduction studies utilizing SECTRAL doses that were, respectively, approximately 31.5 and 6.8 times the maximum recommended human dose. At this dose in the rabbit, slight fetal growth retardation was noted; this was considered to be a result of maternal toxicity (evidenced by reduced food intake, lowered rate of body weight gain, mortality). Diacetolol studies (doses up to 450 mg/kg/d in rabbits and up to 1800 mg/kg/d in rats) showed no evidence of fetal harm other than a significant elevation in postimplantation loss with 450 mg/kg/d, a level at which food consumption and body weight gain were reduced in rabbit dams; there was a nonstatistically significant increase in incidence of bilateral cataract in rat fetuses from dams treated with 1800 mg/kg/d. There are no adequate and well-controlled trials in pregnant women; SECTRAL should be used during pregnancy only if potential benefit justifies risk to the fetus.

Nonteratogenic Effects: Human studies indicate that acebutolol and diacetolol cross the placenta. Neonates of mothers who received acebutolol during pregnancy have reduced birth weight, decreased blood pressure, and decreased heart rate.

Labor and Delivery: Effect on labor and delivery in pregnant women is unknown. Animal studies have shown no effect of SECTRAL on the usual course of labor and delivery.

Nursing Mothers: Acebutolol and diacetolol appear in breast milk (milk: plasma ratio of 7.1 and 12.2, respectively). Use in nursing mothers is not recommended.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: SECTRAL is well tolerated in properly selected patients. Most adverse effects have been mild, not required therapy discontinuation, and tended to decrease as treatment duration increases.

The incidence of treatment-related side effects (volunteered and elicited) derived from U.S. controlled clinical trials in patients with hypertension, angina and arrhythmia follows. Numbers represent percentage incidence for SECTRAL (N =1002) versus placebo (N=314), respectively.

Cardiovascular: Chest pain 2%, 1%; Edema 2%, 1%. *CNS:* Depression 2%,1%; Dizziness 6%, 2%; Fatigue 11%, 4%; Headache 6%, 4%; Insomnia 3%, 1%; Abnormal dreams 2%, 1%. *Dermatologic:* Rash 2%, 1%. *Gastrointestinal:* Constipation 4%, 0%; Diarrhea 4%, 1%; Dyspepsia 4%, 1%; Flatulence 3%, 1%; Nausea 4%, 0%. *Genitourinary:* Micturition (frequency) 3%, <1%. *Musculoskeletal:* Arthralgia 2%, 2%; Myalgia 2%, 0%. *Respiratory:* Cough 1%, 0%; Dyspnea 4%, 2%; Rhinitis 2%, <1%. *Special Senses:* Abnormal Vision 2%, 0%.

The following selected (potentially important) side effects were seen in up to 2% of SECTRAL patients: *Cardiovascular:* hypotension, bradycardia, heart failure. *CNS:* anxiety hyper/hypoesthesia, impotence. *Skin:* pruritus. *Gastrointestinal:* vomitting, abdominal pain. *Genitourinary:* dysuria, nocturia. *Liver and Biliary:* small number of reported cases of liver abnormalities (increased SGOT, SGPT, LDH). In some cases, increased bilirubin or alkaline phosphatase, fever, malaise, dark urine, anorexia, nausea, headache, and/or other symptoms have been reported. In some cases, symptoms and signs were confirmed by rechallenge. Abnormalities were reversible upon drug cessation. *Musculoskeletal:* back and joint pain. *Respiratory:* pharyngitis, wheezing. *Special Senses:* conjunctivitis, dry eye, eye pain. *Autoimmune:* extremely rare reports of systemic lupus erythematosis.

Incidence of drug-related adverse effects (volunteered and solicited) based on SECTRAL dose is shown below. (Data from 266 hypertensive patients treated for 3 months on a constant dose.)

Body System	400 mg/day (N = 132)	800 mg/day (N = 63)	1200 mg/day (N = 71)
Cardiovascular	5%	2%	1%
Gastrointestinal	3%	3%	7%
Musculoskeletal	2%	3%	4%
Central Nervous System	9%	13%	17%
Respiratory	1%	5%	6%
Skin	1%	2%	1%
Special Senses	2%	2%	6%
Genitourinary	2%	3%	1%

Potential Adverse Effects: Certain adverse effects not listed above have been reported with other β-blocking agents and should be considered as potential adverse effects of SECTRAL.

CNS: Reversible mental depression progressing to catatonia, an acute syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.

Cardiovascular: Intensification of AV block (see CONTRAINDICATIONS). *Allergic:* Erythematous rash, fever with aching and sore throat, laryngospasm, respiratory distress.

Hematologic: Agranulocytosis, nonthrombocytopenic and thrombocytopenic purpura.

Gastrointestinal: Mesenteric arterial thrombosis, ischemic colitis.

Miscellaneous: Reversible alopecia, Peyronie's disease. The oculomucocutaneous syndrome associated with practolol has not been reported with SECTRAL.

Keep at room temperature, Approximately 25°C (77°F).

3482-5 6/21/89

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CORONARY ARTERY DISEASE

The American Journal of Cardiology

SEPTEMBER 15, 1992, VOL. 70, NO. 7

Identification of Viable Myocardium by Dipyridamole-Induced Improvement in Regional Left Ventricular Function Assessed by Echocardiography in Myocardial Infarction and Comparison with Thallium Scintigraphy at Rest

Eugenio Picano, MD, Paolo Marzullo, MD, Guido Gigli, MD, Barbara Reisenhofer, MD, Oberdan Parodi, MD, Alessandro Distante, MD, and Antonio L'Abbate, MD

In patients with coronary artery disease and left ventricular impairment, the distinction between ventricular dysfunction due to myocardial fibrosis and postischemic, viable, although dyssynergic, myocardium has important clinical implications. Experimental studies have shown that dipyridamole can increase myocardial function in stunned segments, outlining a potential role of dipyridamole-induced functional recovery as an ultrasonic marker of myocardial viability. The aim of this study was to assess whether the increase of regional left ventricular function early during dipyridamole infusion in basally asynergic segments could identify viable myocardium recognized by rest injected, delayed (>14 hours from tracer injection) thallium and (in a subset of patients) late functional recovery evaluated by a follow-up echocardiogram at rest. Twenty-two patients with angiographically documented coronary artery disease and regional dysfunction in resting conditions (average left ventricular ejection fraction 43 ± 8%) were studied by echocardiography. All patients underwent a dipyridamole-echocardiographic test (up to 0.84 mg/kg over 10 minutes) and a delayed planar thallium study. A 13-segment model was used for both techniques. A score index ranging from 1 (normokinesia) to 4 (dyskinesia) was used for echocardiography. Thallium-201 activity was expressed in each segment as the percentage of maximal activity in the corresponding view. After dipyridamole, the wall motion score was assigned to each segment in resting conditions and at peak hyperkinesia before possible mechanical signs of ischemia. A segment was considered viable when there was a regional activity >55% of peak thallium and when a resting dyssynergy (echocardiographic score ≥2) showed an improvement of ≥1 grade by dipyridamole. In all, 80 basally asynergic segments were scored. Dipyridamole and thallium had concordant results in 21 of 26 thallium-viable and 52 of 54 thallium-necrotic segments. The 23 segments viable by dipyridamole had a higher thallium score than did the 57 necrotic by dipyridamole (73 ± 9 vs 42 ± 9; p <0.01). In a subset of 15 patients, a follow-up echocardiogram at rest was obtained at 3.4 ± 2.7 months after the initial study. A significant functional recovery (improvement of ≥1 grade) was found in 15 of 19 segments with and only 5 of 39 without dipyridamole-induced improvement (79 vs 13%; p <0.01). These observations suggest that dipyridamole-induced recovery in the contractile function of basally asynergic segments (possibly linked to the inotropic effect of increased flow) identifies areas with myocardial viability.

(Am J Cardiol 1992;70:703–710)

In patients with coronary artery disease and impaired left ventricular function, the distinction between ventricular dysfunction due to myocardial fibrosis and postischemic, viable, although dyssynergic, myocardium has important clinical implications.[1] An accepted clinical standard for measuring myocardial viability is delayed thallium-201 scintigraphy.[2–5] Only viable cells with intact membranes retain the potassium analogue thallium-201, reflecting the potassium space of viable tissue. The possibility of obtaining reliable information on viability by means of echocardiography is very attractive in principle, owing to the lower cost, widespread availability, and nonionizing and environment-friendly nature of ultrasonic imaging. Viable myocardium can be identified using 2-dimensional echocardiography together with low-dose dobutamine infusion; the improved myocardial thickening of segments dyssynergic in rest-

From the Istituto di Fisiologia Clinica, CNR, Pisa, Italy. Manuscript received March 16, 1992; revised manuscript received and accepted May 20, 1992.

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ing conditions is a sign of viability, whereas necrotic segments show no functional improvement.[6] The occurrence of transient hyperkinesia has been described as the physiologic response to dipyridamole infusion.[7,8] Experimental data support the possibility that such an inotropic stimulus (although acting by mechanisms different from dobutamine) may have a similar role in distinguishing necrotic (nonresponsive) from viable (responsive) segments.[9] Therefore, we performed a dipyridamole-echocardiographic test in 22 consecutive patients referred to the nuclear medicine laboratory for a study of tissue viability by delayed thallium scintigraphy. All patients had angiographically assessed coronary artery disease and dyssynergy at rest, both by ventriculography and echocardiography at rest; 7 were studied early (<3 weeks) after an acute myocardial infarction. In 15 patients, a follow-up echocardiogram was obtained in basal conditions to assess the functional recovery occurring spontaneously or after a revascularization procedure, or both.

METHODS

Patient selection: We studied 22 patients (20 men and 2 women, age range 35 to 69 years, mean 58 ± 7) with angiographically proved coronary artery disease and left ventricular dysfunction. Patients were selected for the study on referral to the nuclear medicine laboratory to establish the presence of viable versus necrotic myocardium in a basally dyssynergic zone. Fifteen patients had evidence of previous (>3 months) myocardial infarction, whereas 7 were studied early (within 3 weeks) after an acute myocardial infarction. The electrocardiographic site of myocardial infarction was inferior in 14 patients (1 with non-Q-wave myocardial infarction) and anterior in 8 (2 with non-Q-wave myocardial infarction).

Coronary arteriography demonstrated significant stenosis (≥75% reduction in luminal diameter) of 1 vessel in 6 patients, 2 vessels in 14, and 3 vessels in 2. Average left ventricular ejection fraction calculated from biplane contrast ventriculography was 43 ± 8%.

Patients underwent thallium scintigraphy and dipyridamole-echocardiography at rest within 1 week (on different days and in random order) either after withdrawal of all antianginal medications (n = 13) or during antianginal therapy (n = 9) with β blockers (n = 2) or calcium antagonists (n = 7) or nitrates (n = 8), or a combination.

A follow-up echocardiogram was obtained in basal conditions in 15 patients 1.5 to 12 months after the initial study (mean 3.5 ± 2.7). Three of these patients were evaluated after revascularization procedures (angioplasty in 2 and coronary artery bypass surgery in 1).

Thallium imaging: Patients were intravenously injected at rest with a mean of 2.5 mCi of thallium-201 followed by a 10 ml flush with saline solution. Delayed imaging at rest began 14 ± 2 hours (range 14 to 18) after the injection in the anterior projection, followed sequentially by 45° and 70° left anterior oblique views. All images were obtained at the 80 KeV photo peak with 30% window and stored on 128 × 128 byte matrix. Approximately 300,000 counts were obtained during 10 minutes for each image, using a small field-of-view mobile gamma camera (APEX 210 M, Elscint, Israel) equipped with a low-energy, high-resolution collimator.

QUALITATIVE ANALYSIS: Excluding basal and valve plane, the thallium images of the left ventricle were divided in 13 segments, according to previously described criteria.[10,11] All segments were visually analyzed by 2 experienced, independent observers (unaware of dipyridamole-echocardiographic test results) who scored raw and background subtracted images obtained using the computer-assisted standard interpolative algorithm.[12] Each segment was coded as having either normal or moderately reduced uptake (grades 1 and 2) or definitely low or absent thallium activity (grades 3 and 4). All segments with a thallium score ≥3 were defined as having myocardial necrosis. Interobserver agreement was complete if both observers graded a region identically; disagreement was complete if the scores differed by 2 points.

QUANTITATIVE REGIONAL MYOCARDIAL THALLIUM-201 ANALYSIS: Computer quantification of thallium-201 images was performed in the same segments used for qualitative analysis. After background subtraction,[12] the count activities within the myocardial sectors were expressed as a percentage of the activity measured in each view. To simplify comparison with the echocardiographic data, all segments were scored as having normal (76 to 100% of peak), moderately reduced (56 to 75%), severely reduced (25 to 55%) or absent (<25%) activity. Thallium-viable and -necrotic segments were grouped according to a percentage peak activity > and <55%, respectively. This value was chosen according to the limit of 2.5 SD below the normal values obtained in our laboratory from normal segments. This cut-off value was also close to that reported by several investigators in a similar study cohort studied by quantitative regional thallium-201 analysis.[5,13]

Dipyridamole-echocardiography: Two-dimensional echocardiographic and 12-lead electrocardiographic monitoring were performed in combination with dipyridamole infusion at an initial rate of 0.56 mg/kg over 4 minutes; this was followed by 4 minutes of observation and then (in case of negative response by echocardiographic criteria) by an additional 0.28 mg/kg in 2 minutes.[14] Therefore, the maximal cumulative dose achieved was 0.84 mg/kg over 10 minutes. Aminophylline, which promptly reverses the effect of dipyridamole, was available. Furthermore, in case of test negativity, aminophylline (40 to 70 mg over 1 minute) was administered at the 15th minute. Two-dimensional echocardiograms were continuously obtained and intermittently recorded during and up to 5 minutes after dipyridamole administration. Commercially available, wide-angle, phased-array imaging systems (Hewlett-Packard 77020, Toshiba Sonolayer FFA270A, or Esaote Biomedica SIM 7000, 2.5 and 3.5 MHz transducers) were used. In the baseline studies as well as during stress, all standard echocardiographic views were obtained when possible.

Videotapes were analyzed by 2 experienced independent observers unaware of the clinical, angiographic and scintigraphic data. When appropriate, a digital acquisi-

tion of images of interest was obtained either on- (by Esaote Biomedica SIM 7000) or off-line by an array-processor–based computer for medical image processing (MIPRON, Kontron, Germany), and a side-by-side display of images at rest and peak stress in a cineloop mode was obtained.

A wall motion score index was derived for rest and peak dipyridamole echocardiograms (0 to 1 minute after the end of each infusion) in all patients. The left ventricle was divided in 13 segments: apex, and proximal and distal septal, anterior, anterolateral, posterolateral, posterior and inferior wall.[15] This segmentation was based on the 20-segment model proposed by the American Society of Echocardiography,[15] with the apex considered as 1 segment and only 2 septal segments taken into account to match the nuclear segmentation. According to the recommendations of the American Society of Echocardiography,[16] segmental wall motion was graded as follows: normal — normal motion at rest, with normal/increased wall motion and systolic thickening (hyperkinesia) after dipyridamole (score = 1); hypokinetic — marked reduction in endocardial motion and systolic thickening (score = 2); akinetic — virtual absence of inward motion and systolic thickening (score = 3); or dyskinetic — paradoxical wall motion away from the center of the left ventricle in systole, or systolic thickening, or both (score = 4). Inadequately visualized segments were not scored.

Statistical analysis: Comparison between regional uptake of thallium and dipyridamole-induced functional changes was performed by means of chi-square analysis. The comparison of wall motion score index at rest, during dipyridamole-induced hyperkinesia and at follow-up was performed by analysis of variance, and subgroup analysis by Scheffè test. Values are expressed as mean ± 1 SD; a p value <0.05 was considered significant.

RESULTS

Thallium imaging: There was complete agreement between the 2 observers in 270 of 286 segments, and in the remaining 14 (5%) a consensus was reached. For quantitative analysis, interobserver agreement was good ($r = 0.95$; $p < 0.001$). Similarly, agreement for the same observer on 2 separate occasions in analyzing the same segment was good ($r = 0.96$; $p < 0.0001$).

In general, qualitative analysis correlated well to quantitative data. Segments scored as necrotic (<55% of peak activity) had a moderate to severe reduction of thallium uptake on visual analysis (grades 3 and 4), whereas viable segments with an uptake >55% of the peak had a visually definite, although reduced in some cases, thallium activity (grades 1 and 2). Only 6 segments (2%) had discrepancies when compared with the relative quantitative values. Three segments with a qualitative score of 2 had a thallium percent activity <55%, and 3 segments with a score of 3 had an activity >55%.

For purposes of comparison with echocardiographic imaging, these discrepant segments were grouped according to quantitative analysis. In the basally dyssynergic segments, qualitative and quantitative thallium assessment of viability versus necrosis were fully concordant.

Examples of viable and necrotic segments by qualitative and quantitative analysis are shown in Figure 1.

Echocardiographic imaging: By inclusion criteria, all patients had a regional dyssynergy in the echocardiogram at rest. Of 286 myocardial segments initially considered in the 22 patients, 22 were considered uninterpretable and 80 were scored as dyssynergic in resting conditions. Of these 80 segments, 23 had an increase of ≥1 grade at peak hyperkinesia, whereas 57 remained unchanged; 73 were scored unanimously by 2 observers, whereas in the remaining 7 a consensus decision was reached. Contractility improvement was observed at the end of the full dose or (in patients with low-dose positivity who did not receive the higher dose) at the end of the lower dose. Examples of necrotic and viable segments as identified by response to dipyridamole are shown in Figures 2 and 3, respectively.

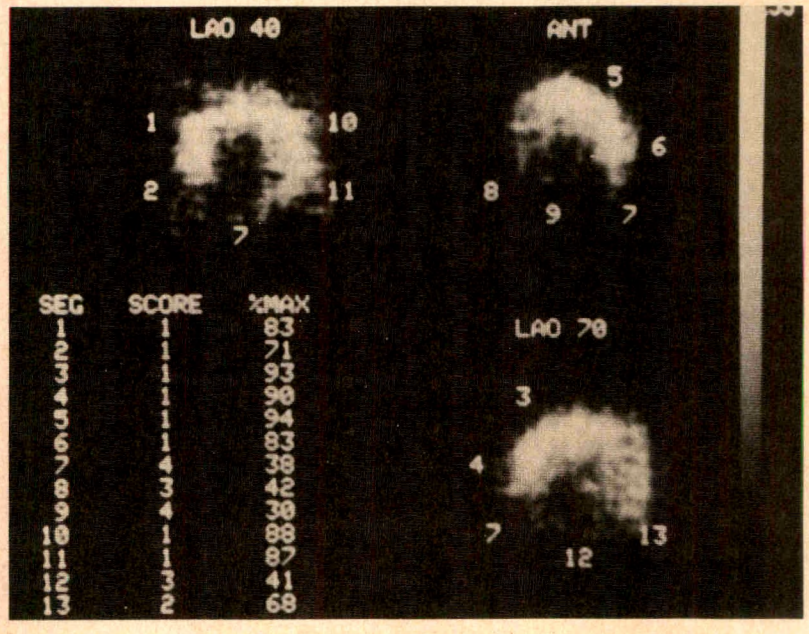


FIGURE 1. Analysis of regional thallium activities performed by dividing planar images into 13 regions of interest, representing proximal and distal anterior (ANT), posterolateral, inferior and anterolateral wall, and the apex. Normal or only moderately reduced activity is evident in all segments (SEG) except 7 to 9 and 12. Quantitative analysis displayed for each segment shows close correlation to qualitative data. LAO = left anterior oblique.

No patient developed limiting side effects or significant complications during dipyridamole-echocardiography. Of 22 studies, 7 were negative and 15 were positive for coronary artery disease; of these 15, 4 were positive in a region remote from the one showing a dyssynergy at rest ("heterozonal positivity"), whereas 11 were positive for either a marked worsening of function in the basally dyssynergic zone or an extension of the dyssynergy to an adjacent segment perfused by the same coronary ("homozonal positivity").

Correlation between dipyridamole-echocardiographic results and coronary angiography: Of 7 patients with negative dipyridamole-echocardiography, 5 had 1- and 2 had 2-vessel disease. Four of these were studied by dipyridamole-echocardiography while receiving full antianginal therapy.

All 12 patients with dipyridamole-echocardiographic homozonal positivity had a critical residual stenosis (≥75%) in the infarct-related vessel.

All 4 patients with dipyridamole-echocardiographic heterozonal positivity had multivessel coronary disease (2-vessel disease in 2 and 3-vessel in 2); 1 also had homozonal positivity.

Correlation between dipyridamole-induced hyperkinesia and thallium uptake at rest: In all, 80 basally asynergic segments were scored. In these segments, qualitative and quantitative thallium assessment of viability versus necrosis was fully concordant. Dipyridamole and thallium showed concordant results in 21 of 26 thallium-viable and 52 of 54 thallium-necrotic segments (Figure 4). The 23 segments viable by dipyridamole had a higher qualitative thallium score than did

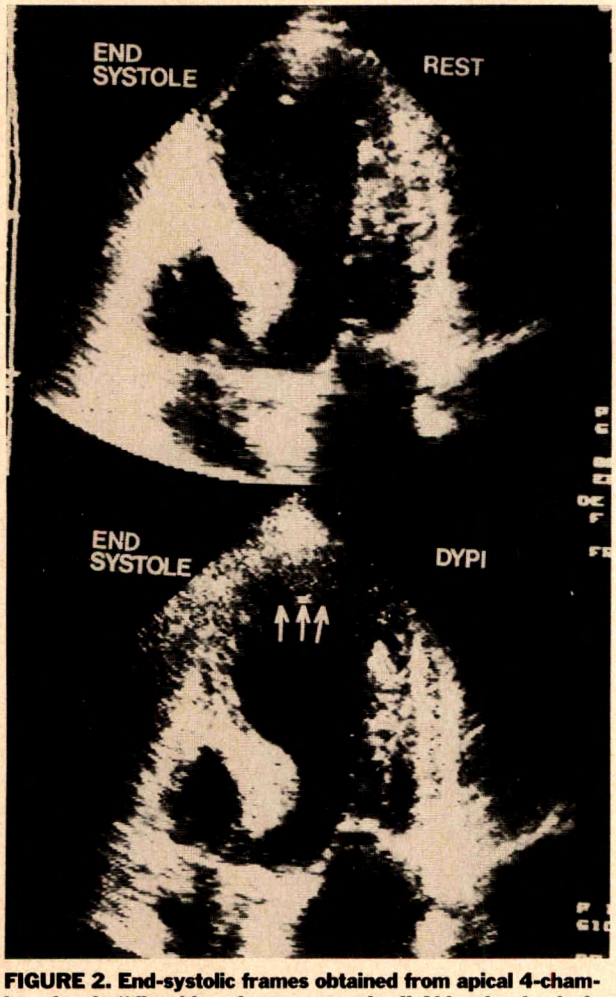


FIGURE 2. End-systolic frames obtained from apical 4-chamber view in "dipyridamole nonresponder." Akinesia of apical and distal septal segments does not improve after dipyridamole (DYPI).

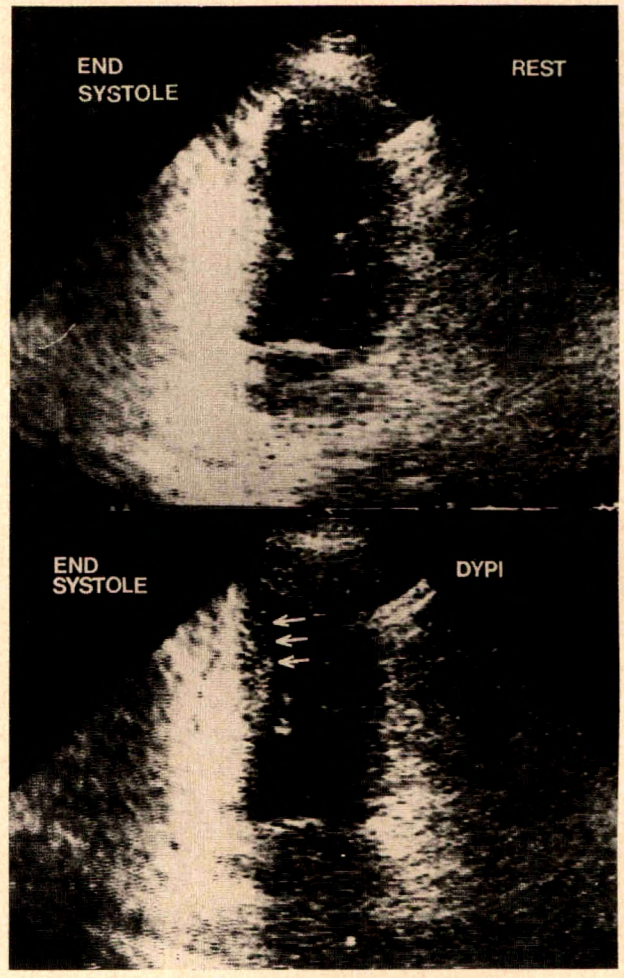


FIGURE 3. End-systolic frames obtained from 2-chamber apical view in "dipyridamole-responder." Akinesia of distal inferior segment markedly improves after dipyridamole (DYPI).

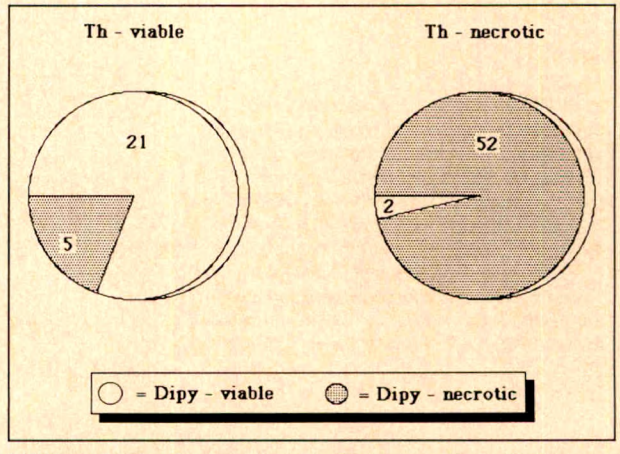


FIGURE 4. *Pie diagram* showing high concordance between assessment of viability by thallium (Th) uptake and functional response to dipyridamole (Dipy) infusion.

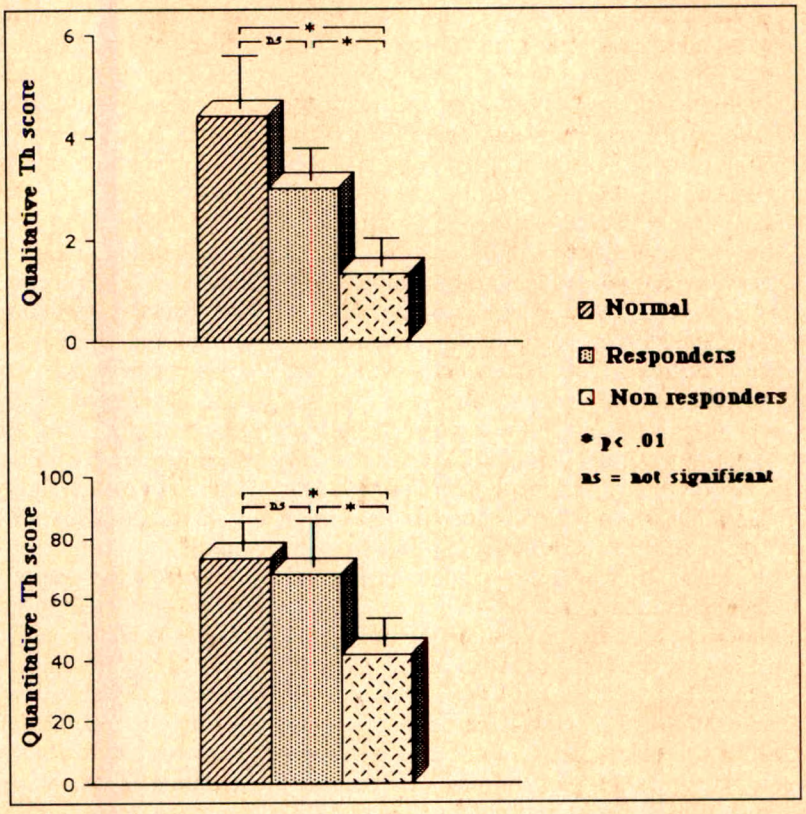


FIGURE 5. Histogram showing that segments identified as "nonresponders" after dipyridamole have lower thallium (Th) score compared with "responders" at both qualitative *(top)* and quantitative *(bottom)* scoring.

the 57 necrotic by dipyridamole (3.2 ± 1.4 vs 1.4 ± 1.4; $p < 0.01$) (Figure 5). When compared with quantitative analysis of thallium-201 distribution, the same dipyridamole-viable and -necrotic segments showed an average percent activity of 73 ± 9% and 42 ± 9%, respectively ($p < 0.01$) (Figure 5).

Correlation between dipyridamole-induced hyperkinesia and delayed functional recovery: In 15 patients, a follow-up echocardiogram was obtained, enabling the evaluation of 58 segments that were dyssynergic in the initial study at rest. Figure 6 shows the changes in the echocardiographic score index between echocardiograms at rest, during dipyridamole infusion and at follow-up at rest in patients with and without dipyridamole-induced functional recovery. Regional wall motion improved in time by ≥1 grade in 15 of 19 segments with and only 5 of 39 without dipyridamole-induced recovery (79 vs 13%; $p < 0.01$).

DISCUSSION

Dipyridamole-induced recovery of contractile function in a segment that is asynergic at rest reliably identifies the tissue viability, independently documented by delayed thallium scintigraphy and late functional recovery. This finding has potentially important pathophysiologic as well as clinical implications.

Mechanisms of dipyridamole-induced recovery of contractile function: The results are in agreement with previous experimental and clinical studies demonstrating that ventricular dysfunction of viable tissue can be improved by inotropic stimulus.[17–22] In these studies, the inotropic stimulus was usually represented by a catecholamine infusion (dopamine,[18,19] isoproterenol,[19] epi-

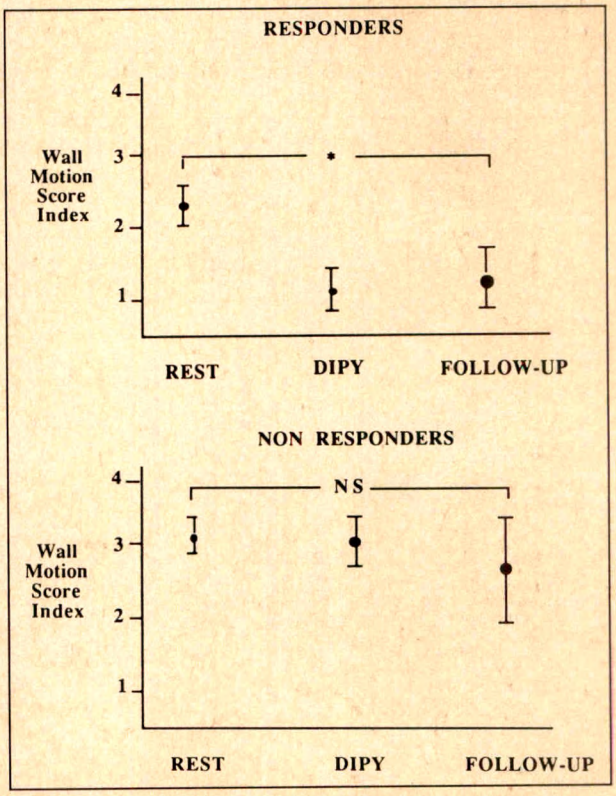


FIGURE 6. Changes in echocardiographic score index between early study at rest, during dipyridamole (DIPY) infusion and at follow-up study for segments showing improvement of ≥1 grade after dipyridamole (responders) and no improvement after dipyridamole (nonresponders). Accordingly, wall motion score index at baseline was significantly higher than at follow-up for responders, whereas nonresponders had similar values at baseline and follow-up. NS = not significant.

nephrine[22] or dobutamine[6]). However, dipyridamole infusion is also an effective inotropic stimulus for stunned myocardium.[9] The potential mechanisms involve adrenergic stimulation (which exists during dipyridamole administration, but of relatively small entity)[23,24] and, more likely, increased flow. The reduced regional function of postischemic myocardium can be selectively enhanced by the increase in coronary blood flow after very low dose dipyridamole infusion (0.06 mg/min for 15 minutes).[9] More recently, the higher dipyridamole dose (0.84 mg/kg over 10 minutes) was shown to be effective in fully normalizing left ventricular dysfunction in areas of stunned myocardium. This mechanical recovery was associated with a fourfold increase in flow.[25] The increase in function is expected on the basis of the known relation between myocardial contractility and coronary perfusion,[26] as originally described by Gregg.[27] Although the mechanism for the Gregg phenomenon is unknown,[26] the most likely explanation involves changes in vascular distention that affect sarcomere length and thereby influence contractility function.[27]

Study limitations: A first limitation of this study stems from the inherent approximation of any attempt to directly compare myocardial segments imaged by 2 different techniques such as planar scintigraphy and 2-dimensional echocardiography. We tried to minimize this problem by using a 13-segment model for both imaging techniques. However, a margin of ambiguity was unavoidable, possibly accounting for some of the discrepancies between the 2 techniques. This potential bias was completely overcome in the follow-up section of the study when a subset of patients was reevaluated by 2-dimensional echocardiography at rest after a variable time interval from the initial study. The regions with dipyridamole-induced functional improvement showed a greater recovery in comparison with the regions with no dipyridamole-induced functional change. In general, however, thallium is a reasonable standard for assessing cell viability, and is only slightly less accurate, if combined with late redistribution or tracer reinjection techniques,[1,5,28] than the more costly and sophisticated positron emission tomographic imaging. In this study, we did not use the reinjection technique after the standard stress-redistribution sequence to define the true metabolic component of thallium-201 independently from possible long-lasting effects of transient ischemia. This is in agreement with the fundamental principles of thallium-201 kinetics and confirms the clinical value of delayed rest protocols for the assessment of viable myocardium.[29]

The clinical use of the echocardiographic information is restricted to patients with acceptable acoustic window in resting conditions; furthermore, even in these patients not all segments can always be visualized. For example, the 22 patients in this study had a good-quality study at rest, but of all segments, 8% could not be reliably scored both at rest and during stress. A further limitation of the study is that 9 of 22 patients were receiving continued antianginal therapy (2 with β blockers) that may have lowered the sensitivity of dipyridamole-echocardiography for detecting coronary artery disease.[30] However, the viability information did

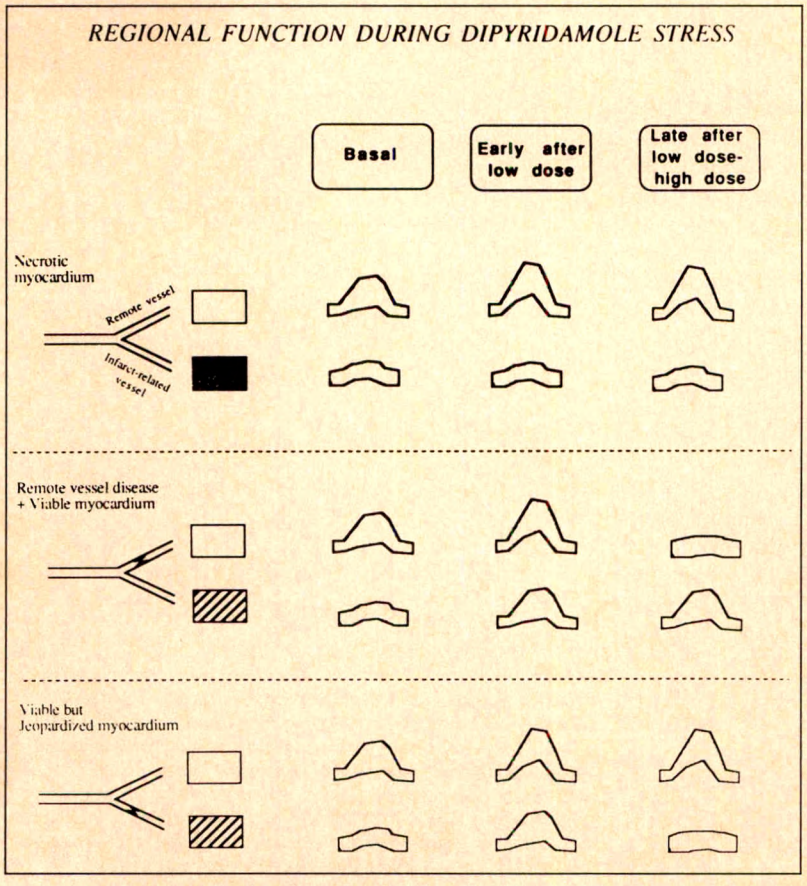


FIGURE 7. Schematic representation of different mechanical patterns during dipyridamole-echocardiography as function of condition of basally asynergic zone (viable vs necrotic) and of anatomic state of infarct-related and remote vessel. Necrotic tissue shows unchanged function throughout test, regardless of underlying anatomic condition of infarct-related vessel. Viable tissue shows early functional recovery. At later stage, there may be marked worsening (or extension, or both) of regional function if significant stenosis is present in infarct-related vessel. Critical stenosis in remote vessel is detected as new dyssynergy in region with normal function at rest.

not appear to be affected by concomitant antianginal therapy. This empirical finding is also in agreement with experimental studies showing that the inotropic effect of dipyridamole is due to increased flow and is not affected by β blockers.[31]

A potential limitation of the study may be the subjective, qualitative evaluation of regional wall motion. However, the diagnostic accuracy is not increased by quantitative methods, because the human eye naturally integrates space and time, and its discriminatory power is very difficult to match and virtually impossible to surpass. Different persons have different eyes, but there is an excellent concordance between experienced observers after a limited learning curve.[32]

Clinical implications: Dipyridamole-echocardiography has been widely used for the diagnosis of coronary artery disease and (even in patients with previous myocardial infarction) is highly feasible, safe and well-tolerated.[33,34] It enables identification of the presence of multivessel disease (detected by heterozonal positivity), as well as the critical residual stenosis in the ischemia-related vessel (detected as homozonal positivity),[35] and patients at high risk of major events.[36] The clinical value of the test is further increased by the viability information that (as shown in the present study) can be obtained on the basis of functional change in the region asynergic at rest, which is similar to what occurs with dobutamine.[37]

In patients with technically adequate echocardiographic recordings, this viability information should be added to the usual information on test positivity or negativity when a dyssynergy at rest is present. The following 3 possible scenarios may be envisaged for a basally dyssynergic region after dipyridamole infusion: its function remains unchanged, improves without later development of ischemia, or transiently improves and later on during the test a functional deterioration occurs in the same region with test homozonal positivity (Figure 7).

Each scenario has its pathophysiologic counterpart with different therapeutic implications. An asynergic segment without improvement indicates a dead zone; the coronary anatomy can range from no disease to complete occlusion, but the territory is no longer vital. In the asynergic region exhibiting functional improvement, there is viable tissue and, if the test is negative for ischemia, either no critical coronary stenosis or effective compensatory collateral circulation can be expected in the infarct-related vessel. However, if regions with dipyridamole-induced functional recovery show positivity for ischemia during the test, the underlying anatomy is of a moderate to severe coronary obstruction, indicating that the tissue is viable but jeopardized.

Acknowledgment: We are grateful to Dr. Fabio Lattanzi, MD, for keen and friendly review of the paper, to Dr. Antonio Caselli, PhD, for editing the manuscript and to Claudia Taddei for secretarial assistance.

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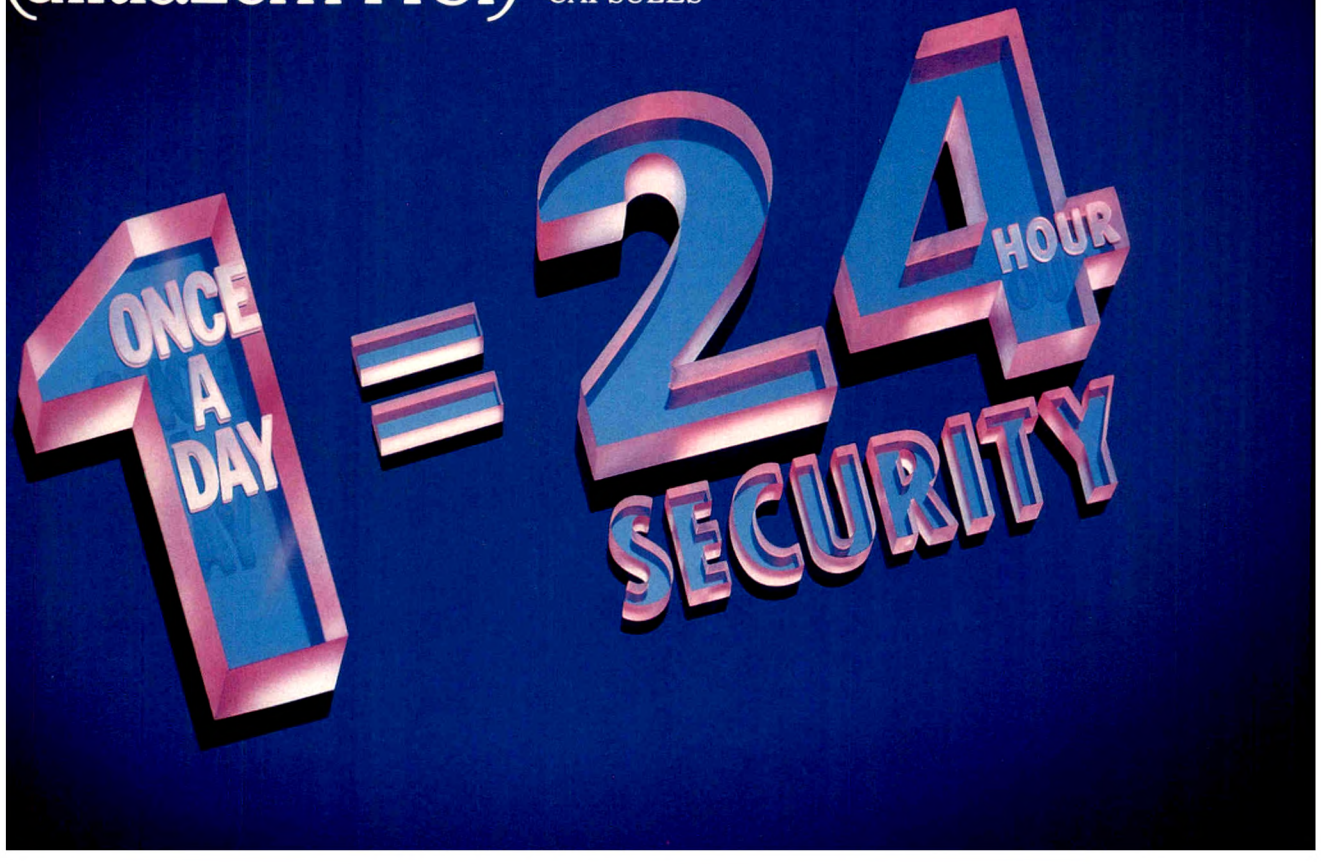
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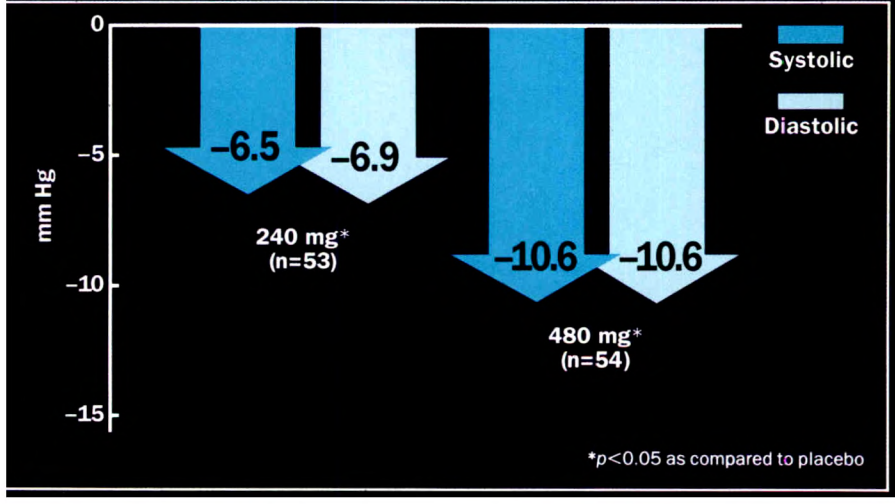
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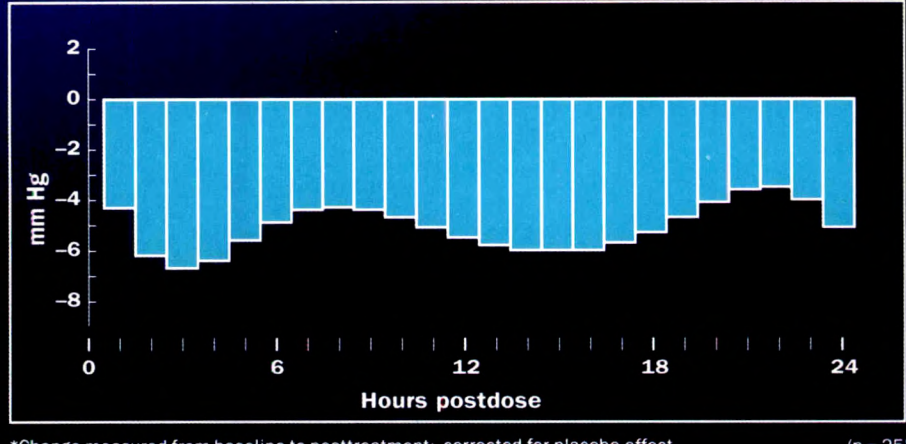
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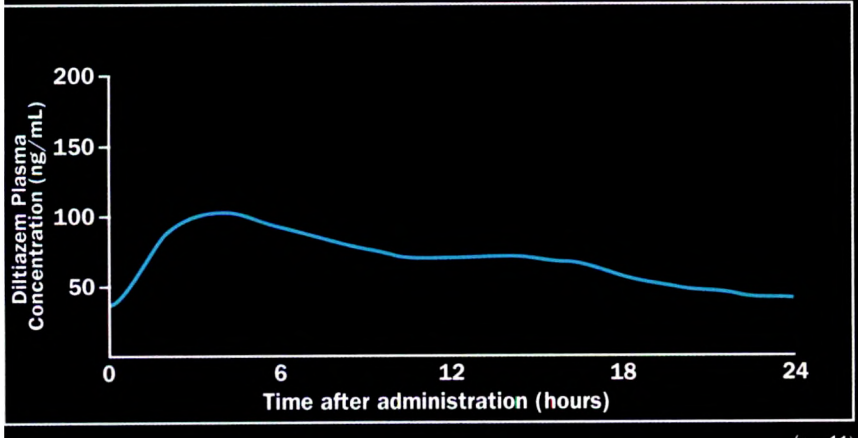
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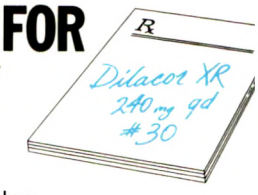
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DILACOR™ XR
(diltiazem HCl) EXTENDED RELEASE CAPSULES





24-HOUR DELIVERY FOR 24-HOUR SECURITY



Both the 180-mg and 240-mg capsules are available at the same price

BRIEF SUMMARY
CONTRAINDICATIONS
Diltiazem hydrochloride is contraindicated in: (1) patients with sick sinus syndrome except in the presence of a functioning ventricular pacemaker; (2) patients with second or third degree AV block except in the presence of a functioning ventricular pacemaker; (3) patients with hypotension (less than 90 mmHg systolic); (4) patients who have demonstrated hypersensitivity to the drug; and (5) patients with acute myocardial infarction and pulmonary congestion as documented by X-ray on admission.

WARNINGS
1. Cardiac Conduction. Diltiazem hydrochloride prolongs AV node refractory periods without significantly prolonging sinus node recovery time, except in patients with sick sinus syndrome. This effect may rarely result in abnormally slow heart rates (particularly in patients with sick sinus syndrome) or second, or third degree AV block (22 of 10,119 patients, or 0.2%); 41% of these 22 patients were receiving concomitant ß-adrenoceptor antagonists versus 17% of the total group. Concomitant use of diltiazem with beta-blockers or digitalis may result in additive effects on cardiac conduction. A patient with Prinzmetal's angina developed periods of asystole (2 to 5 seconds) after a single 60 mg dose of diltiazem.

2. Congestive Heart Failure. Although diltiazem has a negative inotropic effect in isolated animal tissue preparations, hemodynamic studies in humans with normal ventricular function have not shown a reduction in cardiac index nor consistent negative effects on contractility (dp/dt). An acute study of oral diltiazem in patients with impaired ventricular function (ejection fraction of 24% ± 6%) showed improvement in indices of ventricular function without significant decrease in contractile function (dp/dt). Worsening of congestive heart failure has been reported in patients with preexisting impairment of ventricular function. Experience with the use of diltiazem hydrochloride in combination with beta-blockers in patients with impaired ventricular function is limited. Caution should be exercised when using this combination.

3. Hypotension. Decreases in blood pressure associated with diltiazem hydrochloride therapy may occasionally result in symptomatic hypotension.

4. Acute Hepatic Injury. Mild elevations of serum transaminases with and without concomitant elevation in alkaline phosphatase and bilirubin have been observed in clinical studies. Such elevations were usually transient and frequently resolved even with continued diltiazem treatment. In rare instances, significant elevations in alkaline phosphatase, LDH, SGOT, SGPT, and other phenomena consistent with acute hepatic injury have been noted. These reactions tended to occur early after therapy initiation (1 to 6 weeks) and have been reversible upon discontinuation of drug therapy. The relationship to diltiazem is uncertain in some cases, but probable in some others (see PRECAUTIONS).

PRECAUTIONS
General. Diltiazem hydrochloride is extensively metabolized by the liver and is excreted by the kidneys and in bile. As with any drug given over prolonged periods, laboratory parameters should be monitored at regular intervals. The drug should be used with caution in patients with impaired renal or hepatic function. In subacute and chronic dog and rat studies designed to produce toxicity, high doses of diltiazem were associated with hepatic damage. In special subacute hepatic studies, oral doses of 125 mg/kg and higher in rats were associated with the histological changes in the liver which were reversible when the drug was discontinued. In dogs, doses of 20 mg/kg were also associated with hepatic changes; however, these changes were reversible with continued dosing.

Dermatological events (see ADVERSE REACTIONS) may be transient and may disappear despite continued use of diltiazem hydrochloride. However, skin eruptions progressing to erythema multiforme and/or exfoliative dermatitis have also been infrequently reported. Should a dermatologic reaction persist, the drug should be discontinued.

Although Dilacor™ XR utilizes a slowly disintegrating matrix, caution should still be used in patients with preexisting severe gastrointestinal narrowing (pathologic or iatrogenic). There have been no reports of obstructive symptoms in patients with known strictures in association with the ingestion of Dilacor™ XR.

Information for Patients. Dilacor™ XR capsules should be taken on an empty stomach. Patients should be cautioned that the Dilacor™ XR capsules should not be opened, chewed or crushed, and should be swallowed whole.

Drug Interaction. Due to the potential for additive effects, caution and careful titration are warranted in patients receiving diltiazem hydrochloride concomitantly with any agents known to affect cardiac contractility and/or conduction (see WARNINGS). Pharmacologic studies indicate that there may be additive effects in prolonging AV conduction when using beta-blockers or digitalis concomitantly with diltiazem hydrochloride (see WARNINGS). As with all drugs, care should be exercised when treating patients with multiple medications. Diltiazem hydrochloride undergoes biotransformation by cytochrome P-450 mixed function oxidase. Co-administration of diltiazem hydrochloride with other agents which follow the same route of biotransformation may result in the competitive inhibition of metabolism. Dosages of similarly metabolized drugs, such as cyclosporin, particularly those of low therapeutic ratio or in patients with renal and/or hepatic impairment, may require adjustment when starting or stopping concomitantly administered diltiazem hydrochloride to maintain optimum therapeutic blood levels.

Beta-Blockers: Controlled and uncontrolled domestic studies suggest that concomitant use of diltiazem hydrochloride and beta-blockers or digitalis is usually well-tolerated, but available data are not sufficient to predict the effects of concomitant treatment in patients with left ventricular dysfunction or cardiac conduction abnormalities. Administration of diltiazem hydrochloride concomitantly with propranolol in five normal volunteers resulted in increased propranolol levels in all subjects and the bioavailability of propranolol was increased approximately 50%. If combination therapy is initiated or withdrawn in conjunction with propranolol, an adjustment in the propranolol dose may be warranted (see WARNINGS).

Cimetidine: A study in six healthy volunteers has shown a significant increase in peak diltiazem plasma levels (58%) and area-under-the-curve (53%) after a 1-week course of cimetidine at 1,200 mg per day and diltiazem 60 mg per day. Ranitidine produced smaller, nonsignificant increases. The effect may be mediated by cimetidine's known inhibition of hepatic cytochrome P-450, the enzyme system probably responsible for the first-pass metabolism of diltiazem. Patients currently receiving diltiazem therapy should be carefully monitored for a change in pharmacological effect when initiating and discontinuing therapy with cimetidine. An adjustment in the diltiazem dose may be warranted.

Digitalis: Administration of diltiazem hydrochloride with digoxin in 24 healthy male subjects increased plasma digoxin concentrations approximately 20%. Another investigator found no increase in digoxin levels in 12 patients with coronary artery disease. Since there have been conflicting results regarding the effect of digoxin levels, it is recommended that digoxin levels be monitored when initiating, adjusting, and discontinuing diltiazem hydrochloride therapy to avoid possible over- or under-digitalization (see WARNINGS).

Anesthetics: The depression of cardiac contractility, conductivity, and automaticity as well as the vascular dilation associated with anesthetics may be potentiated by calcium channel blockers. When used concomitantly, anesthetics and calcium channel blockers should be titrated carefully.

Carcinogenesis, Mutagenesis, Impairment of Fertility. A 24-month study in rats and an 18-month study in mice showed no evidence of carcinogenicity. There was also no mutagenic response *in vitro* or *in vivo* in mammalian cell assays or *in vitro* in bacteria. No evidence of impaired fertility was observed in male or female rats at oral doses of up to 100 mg/kg/day.

Pregnancy. Category C. Reproduction studies have been conducted in mice, rats, and rabbits. Administration of doses ranging from 4 to 6 times (depending on species) the upper limit of the optimum dosage range in clinical trials (480 mg q.d. or 8 mg/kg q.d. for a 60 kg patient) has resulted in embryo and fetal lethality. These studies have revealed, in one species or another, a propensity to cause abnormalities of the skeleton, heart, retina, and tongue. Also observed were reductions in early individual pup weights and pup survival, prolonged delivery and increased incidence of stillbirths.

There are no well-controlled studies in pregnant women; therefore, use diltiazem hydrochloride in pregnant women only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers. Diltiazem is excreted in human milk. One report suggests that concentrations in breast milk may approximate serum levels. If use of diltiazem hydrochloride is deemed essential, an alternative method of infant feeding should be instituted.

Pediatric Use. Safety and effectiveness in children have not been established.

ADVERSE REACTIONS
Serious adverse reactions to diltiazem hydrochloride have been rare in studies with other formulations, as well as with Dilacor™ XR. It should be recognized, however, that patients with impaired ventricular function and cardiac conduction abnormalities have usually been excluded from these studies.

The most common adverse events (frequency ≥1%) in placebo-controlled, clinical hypertension studies with Dilacor™ XR using daily doses up to 540 mg are listed in the table below with placebo-treated patients included for comparison.

MOST COMMON ADVERSE EVENTS
IN DOUBLE-BLIND, PLACEBO-CONTROLLED HYPERTENSION TRIALS*

Adverse Events (COSTART Term)	Dilacor™ XR n=303 # pts (%)	Placebo n=87 # pts (%)
rhinitis	29 (9.6)	7 (8.0)
headache	27 (8.9)	12 (13.8)
pharyngitis	17 (5.6)	4 (4.6)
constipation	11 (3.6)	2 (2.3)
cough increase	9 (3.0)	2 (2.3)
flu syndrome	7 (2.3)	1 (1.1)
edema, peripheral	7 (2.3)	0 (0.0)
myalgia	7 (2.3)	0 (0.0)
diarrhea	6 (2.0)	0 (0.0)
vomiting	6 (2.0)	0 (0.0)
sinusitis	6 (2.0)	1 (1.1)
asthenia	5 (1.7)	0 (0.0)
pain, back	5 (1.7)	2 (2.3)
nausea	5 (1.7)	1 (1.1)
dyspepsia	4 (1.3)	0 (0.0)
vasodilatation	4 (1.3)	0 (0.0)
injury, accident	4 (1.3)	0 (0.0)
pain, abdominal	3 (1.0)	0 (0.0)
arthrosis	3 (1.0)	0 (0.0)
insomnia	3 (1.0)	0 (0.0)
dyspnea	3 (1.0)	0 (0.0)
rash	3 (1.0)	1 (1.1)
tinnitus	3 (1.0)	0 (0.0)

*Adverse events occurring in 1% or more of patients receiving Dilacor™ XR.

The following additional events (COSTART Terms), listed by body system, were reported infrequently in all subjects and hypertensive patients who received Dilacor™ XR (n=425): Cardiovascular: First-degree AV block, arrhythmia, postural hypotension, tachycardia, pallor, palpitations, phlebitis, ECG abnormality, ST elevation; Nervous System: Vertigo, hypertonia, paresthesia, dizziness, somnolence; Digestive System: Dry mouth, anorexia, tooth disorder, eructation; Skin and Appendages: Sweating, urticaria, skin hypertrophy (nevus); Respiratory System: Epistaxis, bronchitis, respiratory disorder; Urogenital System: Cystitis, kidney calculus, impotence, dysmenorrhea, vaginitis, prostate disease; Metabolic and Nutritional Disorders: Gout, edema; Musculoskeletal System: Arthralgia, bursitis, bone pain; Hemic and Lymphatic Systems: Lymphadenopathy; Body as a Whole: Pain, unevaluable reaction, neck pain, neck rigidity, fever, chest pain, malaise; Special Senses: Amblyopia (blurred vision), ear pain.

OVERDOSAGE OR EXAGGERATED RESPONSE
Overdosage experience with oral diltiazem hydrochloride has been limited. The administration of ipecac to induce vomiting and activated charcoal to reduce drug absorption have been advocated as initial means of intervention. In addition to gastric lavage, the following measures should also be considered:

Bradycardia: Administer atropine (0.60 to 1.0 mg). If there is no response to vagal blockade, administer isoproterenol cautiously.

High-Degree AV Block: Treat as for bradycardia above. Fixed high-degree AV block should be treated with cardiac pacing.

Cardiac Failure: Administer inotropic agents (dopamine or dobutamine) and diuretics.

Hypotension: Vasopressors (*e.g.* dopamine or levarterenol bitartrate).

Actual treatment and dosage should depend on the severity of the clinical situation as well as the judgment and experience of the treating physician.

Due to extensive metabolism, plasma concentrations after a standard dose of diltiazem can vary over tenfold, which significantly limits their value in evaluating cases of overdosage.

Charcoal hemoperfusion has been used successfully as an adjunct therapy to hasten drug elimination. Overdoses with as much as 10.8 gm of oral diltiazem have been successfully treated using appropriate supportive care.

CAUTION: FEDERAL (U.S.A.) LAW PROHIBITS DISPENSING WITHOUT PRESCRIPTION.

Please see product circular for full prescribing information.

References:
1. Data on file, Rhône-Poulenc Rorer Pharmaceuticals Inc.
2. *1992 Drug Topics® Red Book® Update.* Oradell, NJ, Medical Economics Co. Inc.; April, 1992.

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Doppler Echocardiographic Patterns of Left Ventricular Filling in Patients Early After Acute Myocardial Infarction

Adrian Chenzbraun, MD, Andre Keren, MD, and Shlomo Stern, MD

Diastolic function is routinely assessed using Doppler-derived left ventricular (LV) filling patterns. Ratios between peak flow velocities during early filling and atrial contraction (E/A) of <1 are considered pathologic and diagnostic of impaired relaxation. Myocardial stiffness can normalize the E/A ratio, and thus, in some clinical settings, a normal E/A ratio may identify patients with high filling pressures. LV filling patterns were studied with Doppler echocardiography in 15 healthy subjects and 38 patients with recent acute myocardial infarction. The results were correlated with clinical and hemodynamic variables. E/A ratio <1 was found in 14 patients (37%) and in only 1 control subject; E/A ratio >2 was found in 5 patients (13%) and in only 1 control subject; 19 patients (50%) had an apparently normal E/A ratio. No correlation was found between LV filling pattern and ejection fraction or presence of diabetes or arterial hypertension. LV end-diastolic pressures were low to normal in patients with an E/A ratio <1 and were usually >15 mm Hg in those with normal or abnormally increased (>2) E/A ratios. Thus, an apparently normal E/A ratio in patients after myocardial infarction may identify those with more severe LV diastolic dysfunction and increased LV filling pressure.

(Am J Cardiol 1992;70:711–714)

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Few data are available on diastolic function in patients recovering after recent acute myocardial infarction.[1] Previous investigations evaluated the diastolic dysfunction of patients in either the acute[2] or chronic[3–6] phase of myocardial infarction. Doppler echocardiography provides a readily available noninvasive method to examine left ventricular (LV) diastolic function[7–9] in patients with coronary artery disease.[2–5,10–12] This study examines the Doppler patterns of LV filling in patients after myocardial infarction before hospital discharge, with reference to hemodynamic parameters.

METHODS

Study cohort: Thirty-eight patients (31 men and 7 women, aged 31 to 75 years, mean 56 ± 11) with acute myocardial infarction underwent Doppler echocardiographic evaluation before discharge. The diagnosis of acute myocardial infarction was made if the patient had typical chest pain lasting >30 minutes, characteristic electrocardiographic changes and a typical creatine-phosphokinase curve. By standard electrocardiographic criteria, 20 patients had anterior, 13 inferior and 5 non-Q-wave infarctions. Systemic arterial hypertension, diabetes mellitus, or both, were present in 13 patients. Mean LV ejection fraction by radionuclide ventriculography was 43 ± 9%. Patients had to be aged <75 years and in sinus rhythm, with normal PR interval and heart rate of 60 of 90 beats/min at the time of echocardiographic evaluation. Clinical condition had to be sufficiently stable to allow for the interruption of diuretics, calcium antagonists, vasodilators, digoxin and antiarrhythmic drugs ≥72 hours before the study without occurrence of congestive heart failure or angina during this time interval. Aspirin, sublingual nitrates (if needed) and β blockers started in 14 patients before inclusion in the study were allowed. No patient received short-acting nitrates on the day of echocardiographic evaluation. Patients with LV hypertrophy (echocardiographic wall thickness >13 mm), more than mild mitral or aortic regurgitation by Doppler color flow study, mitral stenosis of any degree, or aortic stenosis with peak velocity >2 m/s were excluded. Fifteen healthy subjects (aged 41 to 74 years, mean 49 ± 9) with normal clinical, echocardiographic and stress test examinations were used as a control group.

The following data were correlated with the Doppler findings: age, LV ejection fraction by radionuclide ventriculography, LV end-diastolic pressure by catheterization, ischemic response during predischarge treadmill test, and presence of systemic hypertension or diabetes mellitus.

TABLE I Filling Patterns in Patients and Control Subjects

	E/A	ISVRT (ms)	DT (ms)	E/A <1 (n)	E/A >2 (n)
Pts. (n = 38)	1.27	94	159	14	5
Control subjects (n = 15)	1.47	86	172	1	1
p value	NS	NS	NS	<0.05	NS

DT = deceleration time; E/A = ratio of peak velocity of early and late diastolic flow; ISVRT = isovolumic relaxation time; NS = not significant.

TABLE II Hemodynamic and Doppler Findings in 24 Patients

	Age (yr)	ISVRT (ms)	DT (ms)	EF (%)	LVEDP (mm Hg)
E/A >1 (n = 16)	52 ± 11	80 ± 26	155 ± 33	44 ± 9	21 ± 8
E/A <1 (n = 8)	63 ± 7	114 ± 28	165 ± 37	44 ± 6	12 ± 3
p value	<0.001	0.001	NS	NS	0.003

EF = ejection fraction; LVEDP = left ventricular end-diastolic pressure; other abbreviations as in Table I.

Doppler echocardiography: Ultrasound imaging and Doppler analysis were performed as part of the predischarge evaluation at 11 ± 7 days after the acute event, using a 70200A Hewlett-Packard, commercially available, ultrasound machine. Recordings were obtained within 24 hours of cardiac catheterization, and in 5 cases during the catheterization, before injection of contrast material. After standard echocardiographic views were obtained, pulsed Doppler technique using a 2.5 MHz combined imaging Doppler transducer was used to evaluate the mitral flow velocity pattern. The Doppler sample volume (0.25 cm) was positioned at the tips of the mitral leaflets at a point at which the maximal early velocity was recorded; angle correction was not used. Recordings were obtained on a strip chart at 100 mm/s paper speed, together with the phonocardiogram and electrocardiogram. The following LV filling parameters were measured (Figure 1): isovolumic relaxation time, from the aortic component of the second heart sound to the beginning of the mitral flow; peak flow velocity during early filling (E); deceleration time from peak early velocity to intersection of the deceleration slope with the baseline; peak flow velocity during atrial contraction (A); and E/A ratio. Three cycles were measured at end-expiration and averaged for each parameter. Based on the values of Doppler parameters found in the control group, we considered an E/A ratio <1 as pathologically low, whereas a ratio >2 was considered abnormally high.

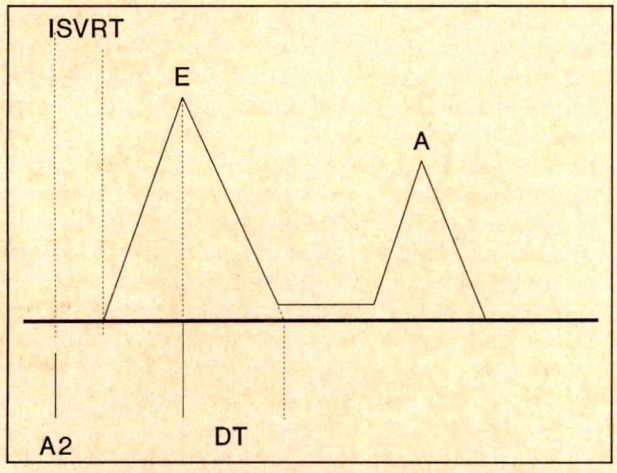


FIGURE 1. Technique for measurement of left ventricular filling parameters using pulsed-wave Doppler mitral flow velocity signal. A = peak velocity of late diastolic flow; A2 = aortic component of second heart sound; DT = deceleration time; E = peak velocity of early diastolic flow; ISVRT = isovolumic relaxation time.

Reproducibility: 18 patients underwent 2 consecutive Doppler studies separated by 4 days. The studies were performed by the same technician and reviewed by the same physician. Care was taken to place the transducer at the same chest location, and data were analyzed for reproducibility only if there was <20% change in blood pressure or heart rate.

Cardiac catheterization: Coronary angiography and left ventriculography were performed in 24 patients using the Judkins technique. Catheterization was not performed in the remaining 14 patients, because of technical reasons not related to clinical condition. Pressure measurements were obtained with fluid-filled catheters, and particular care was taken to obtain good-quality tracings of LV end-diastolic pressure. One-vessel coronary disease was found in 9 patients and multivessel disease in 15. Mean LV end-diastolic pressure was 18 mm Hg.

Treadmill tests: Thirty-three patients performed a modified stress test[13] within 1 day of the echocardiographic examination. The test was positive for ischemia (>1 mm horizontal ST depression at 0.08 second from the J point) in 15 patients.

Statistical analysis: Statistical analysis was performed by Student's *t* test for continuous variables and chi-square test for categoric variables, using a Minitab 7.1 statistical software package.

RESULTS

Reproducibility: Day-to-day reproducibility was good for E/A ratio (r = 0.9) and isovolumic relaxation time (r = 0.64), but poor for deceleration time.

Filling patterns: LV filling parameters in patients and control subjects are shown in Table I. Patients had a tendency toward a prolonged isovolumic relaxation time and a lower E/A ratio compared with those of control subjects, but the differences were not statistically significant. Fourteen patients (37%) had an E/A ratio <1, whereas this value was found in only 1 control subject. Five patients (13%) had abnormally high E/A ratios ranging from 2 to 3, compared with only 1 control subject. Nineteen patients (50%) had an apparently normal E/A ratio. E/A ratio and isovolumic relaxation time were inversely correlated (r = 0.6; p <0.001), whereas no correlation was found between isovolumic relaxation time and deceleration time or between E/A ratio and deceleration time.

Comparison of patients with an E/A ratio <1 with those who had a ratio >1 showed that a ratio <1 was associated with older age, prolongation of isovolumic relaxation time, and lower LV end-diastolic pressures

(Table II). A correlation ($r = 0.63$; $p = 0.006$) was found between E/A ratio and LV end-diastolic pressure (Figure 2). Only 2 patients with an E/A ratio <1 had an LV end-diastolic pressure >15 mm Hg, and an E/A ratio >1 was found in only 2 patients with LV end-diastolic pressure <15 mm Hg. The lowest and thus apparently the most pathologic E/A ratio (0.5) was found in the patient with the lowest end-diastolic pressure (Figure 3a); the highest ratio was found in the patient with the highest LV end-diastolic pressure (Figure 3b). Ejection fraction (Table II), presence of hypertension or diabetes mellitus, and ischemic response during stress test did not correlate with an impaired relaxation pattern (defined as E/A ratio <1).

DISCUSSION

In previous Doppler studies of patients with myocardial infarction,[2–4] data were reported as mean values for both patients and control subjects. Thus, the prevalence of an abnormal E/A ratio in patients after myocardial infarction is not available. To our knowledge, this is the first study that reports the prevalence of Doppler patterns of diastolic dysfunction in patients after infarction before hospital discharge, with reference to clinical and hemodynamic variables.

Using 1 as a cutoff point between normal and low E/A ratio values is arbitrary. However, this criterion reflects common practice and is in accordance with the results obtained in our control subjects, only 1 of whom had a ratio <1. Using this criterion, the prevalence of impaired relaxation in our patients was 37%, but filling pressures were consistently low in these patients. An E/A ratio >1 and its progressive increase to 3 were associated with increased filling pressures. An LV end-diastolic pressure of 15 mm Hg was the cutoff point between patients with an E/A ratio < and >1 in this

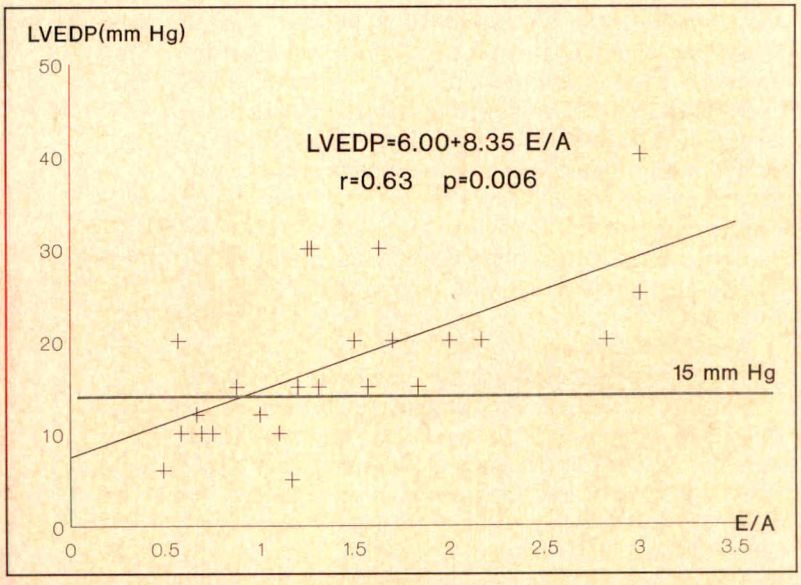


FIGURE 2. Correlation between ratio of peak velocity of early and late diastolic flow (E/A) and left ventricular end-diastolic pressure (LVEDP) in 24 patients with recent myocardial infarction.

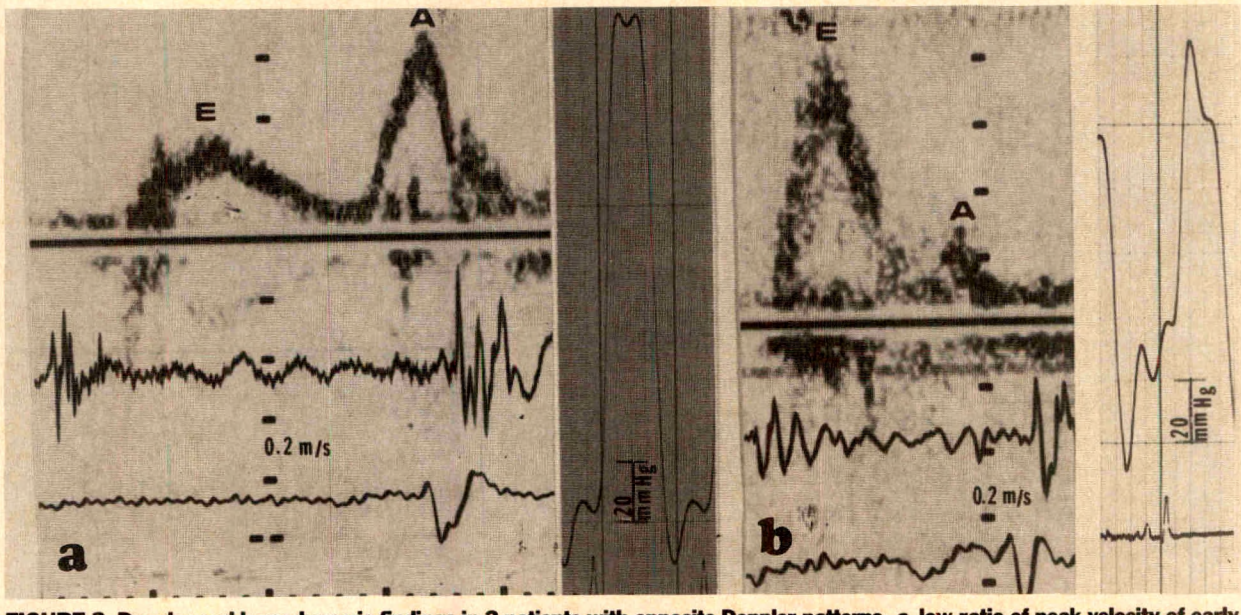


FIGURE 3. Doppler and hemodynamic findings in 2 patients with opposite Doppler patterns. *a*, low ratio of peak velocity of early (E) and late (A) diastolic flow associated with low left ventricular end-diastolic pressure; *b*, high ratio associated with high pressure.

series. It has been shown that in severe diastolic dysfunction associated with high filling pressures, "pseudonormalization" of the filling pattern may occur.[14] Loading conditions can also influence the Doppler pattern of ventricular filling.[15-16] Thus, the result of the effects of impaired myocardial relaxation and increased LV stiffness is complex and results in E/A ratios varying from <1 to a restrictive pattern with a ratio >1, and shortened isovolumic relaxation period in patients with stiff left ventricles.[17] This positive correlation between E/A ratio and end-diastolic pressure was reported in previous studies in animals,[18] and in patients with dilated cardiomyopathy,[19] ischemic heart disease[20,21] and aortic stenosis.[22] In the present study, age was the only clinical variable that correlated with an impaired filling pattern, in accordance with the known changes in diastolic function in elderly subjects.[23-25] The absence of correlation found by us between ejection fraction and Doppler filling patterns is not surprising. Radionuclide studies in patients with myocardial infarction[1,6] showed a positive correlation between systolic and diastolic function. These studies found a good correlation between peak filling rate and ejection fraction by radionuclide ventriculography. However, Doppler indexes (such as E/A ratio) that reflect atrioventricular pressure gradient may act differently than do radionuclide filling indexes. Johannessen et al[5] found that larger infarctions were associated with reduced peak filling rate by radionuclide angiography, but with increased E/A ratio by Doppler.

Study limitations: Patients with either congestive heart failure or ongoing ischemia in whom the clinical condition did not enable cardiac medications to be stopped or reduced to β blockers or short-acting nitrates were not included in the study group, which thus represents a selected cohort. Only 24 of 38 patients had hemodynamic data for correlation with the Doppler patterns. Because this was due to logistical reasons only, there is no selection bias here, and we believe the results are representative for the entire group. Measurements were obtained with fluid-filled catheters, which are obviously less accurate than those with manometer-tipped high-fidelity catheters; however, the quality of the tracings was good, and because we were interested only in the value of LV end-diastolic pressure and not in the morphology of the pressure waveform, we think this should not be viewed as a limitation. The control subjects were slightly younger than the patients (49 ± 9 vs 56 ± 11 years; $p < 0.05$), but an age difference of this order, although statistically significant, is not expected to significantly influence the filling patterns.[14]

Acknowledgment: We thank Richard L. Popp, MD, from Stanford, California, for critical review of the manuscript.

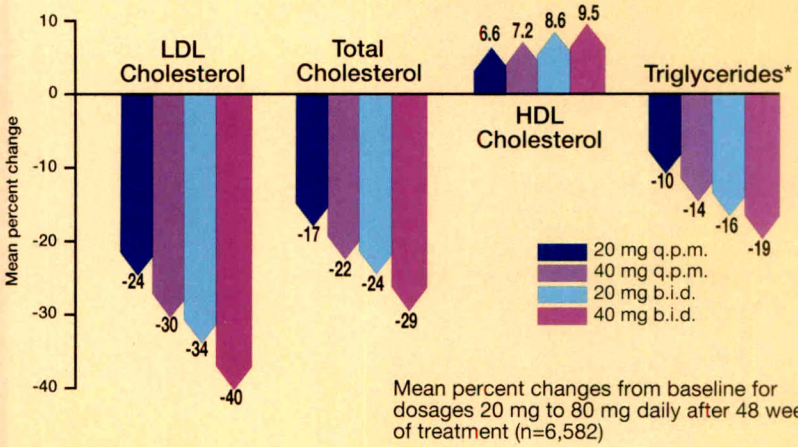
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The largest U.S. double-blind, placebo-controlled trial of patients with moderate hypercholesterolemia

8,245 patients | 362 clinical sites | 48 weeks

Excellent efficacy in lowering LDL and total cholesterol[1]



Mean percent changes from baseline for dosages 20 mg to 80 mg daily after 48 weeks of treatment (n=6,582)

EXPANDED CLINICAL EVALUATION OF LOVASTATIN — THE EXCEL STUDY

* Triglyceride values are expressed as median changes.

1. Bradford, R.H. et al.: Expanded clinical evaluation of lovastatin (EXCEL) study results: I. Efficacy in modifying plasma lipoproteins and adverse event profile in 8,245 patients with moderate hypercholesterolemia, Arch. Intern. Med. *151*:43-49, January 1991.

For many patients with primary hypercholesterolemia (Types IIa and IIb) when diet and other nondrug therapies are inadequate

MEVACOR®
(LOVASTATIN)

Tablets: 10 mg, 20 mg, 40 mg

Proven in research. Proven in practice.

MSD
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MEVACOR is contraindicated in patients who are hypersensitive to any component of the medication; in patients with active liver disease or unexplained persistent transaminase elevations; in pregnant or lactating patients; and in women of childbearing age, except when such patients are highly unlikely to conceive.

For complete details on MEVACOR, including cautionary information regarding myopathy, drug interactions, and liver enzyme monitoring, please refer to the Prescribing Information.

For a brief summary of Prescribing Information, please see the next page of this advertisement.

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MEVACOR® *
(LOVASTATIN)

CONTRAINDICATIONS: Hypersensitivity to any component of this medication.

Active liver disease or unexplained persistent elevations of serum transaminases (see WARNINGS).

Pregnancy and lactation.

Atherosclerosis is a chronic process, and the discontinuation of lipid-lowering drugs during pregnancy should have little impact on the outcome of long-term therapy of primary hypercholesterolemia. Moreover, cholesterol and other products of the cholesterol biosynthesis pathway are essential components for fetal development, including synthesis of steroids and cell membranes. Because of the ability of inhibitors of HMG-CoA reductase such as MEVACOR to decrease the synthesis of cholesterol and possibly other products of the cholesterol biosynthesis pathway, MEVACOR may cause fetal harm when administered to a pregnant woman. Therefore, lovastatin is contraindicated during pregnancy. Lovastatin should be administered to women of childbearing age only when such patients are highly unlikely to conceive. If the patient becomes pregnant while taking this drug, lovastatin should be discontinued, and the patient should be apprised of the potential hazard to the fetus.

WARNINGS: *Liver Dysfunction:* Marked persistent increases (to more than 3 times the upper limit of normal) in serum transaminases occurred in 1.9% of adult patients who received lovastatin for at least 1 year in early clinical trials (see ADVERSE REACTIONS). When the drug was interrupted or discontinued in these patients, the transaminase levels usually fell slowly to pretreatment levels. The increases usually appeared 3 to 12 months after the start of therapy with lovastatin and were not associated with jaundice or other clinical signs or symptoms. There was no evidence of hypersensitivity. In the EXCEL study (see CLINICAL PHARMACOLOGY, *Clinical Studies* in the full Prescribing Information), the incidence of marked persistent increases in serum transaminases over 48 weeks was 0.1% for placebo, 0.1% at 20 mg/day, 0.9% at 40 mg/day, and 1.5% at 80 mg/day in patients on lovastatin. However, in post-marketing experience with MEVACOR, symptomatic liver disease has been reported rarely at all dosages (see ADVERSE REACTIONS).

It is recommended that liver function tests be performed during therapy with lovastatin. Serum transaminases, including ALT (SGPT), should be monitored before treatment begins, every 6 weeks during the first 3 months, every 8 weeks during the remainder of the first year, and periodically thereafter (e.g., at approximately 6-month intervals). Special attention should be paid to patients who develop elevated serum transaminase levels, and, in these patients, measurements should be repeated promptly and then performed more frequently. If the transaminase levels show evidence of progression, particularly if they rise to 3 times the upper limit of normal and are persistent, the drug should be discontinued. Liver biopsy should be considered if elevations are persistent beyond the discontinuation of the drug.

The drug should be used with caution in patients who consume substantial quantities of alcohol and/or have a past history of liver disease. Active liver disease or unexplained transaminase elevations are contraindications to the use of lovastatin.

As with other lipid-lowering agents, moderate (less than 3 times the upper limit of normal) elevations of serum transaminases have been reported following therapy with MEVACOR (see ADVERSE REACTIONS). These changes appeared soon after initiation of therapy with MEVACOR, were often transient, were not accompanied by any symptoms, and interruption of treatment was not required.

Skeletal Muscle: **Rhabdomyolysis has been associated with lovastatin therapy alone, when combined with immunosuppressive therapy including cyclosporine in cardiac transplant patients, and when combined in non-transplant patients with either gemfibrozil or lipid-lowering doses (≥1g/day) of nicotinic acid. Some of the affected patients had preexisting renal insufficiency, usually as a consequence of long-standing diabetes. Acute renal failure from rhabdomyolysis has been seen more commonly with the lovastatin-gemfibrozil combination and has also been reported in transplant patients receiving lovastatin plus cyclosporine.**

Rhabdomyolysis with or without renal impairment has been reported in seriously ill patients receiving erythromycin concomitantly with lovastatin. Therefore, patients receiving concomitant lovastatin and erythromycin should be carefully monitored.

Fulminant rhabdomyolysis has been seen as early as 3 weeks after initiation of combined therapy with gemfibrozil and lovastatin, but may be seen after several months. For these reasons, it is felt that, in most subjects who have had an unsatisfactory lipid response to either drug alone, the possible benefits of combined therapy with lovastatin and gemfibrozil do not outweigh the risks of severe myopathy, rhabdomyolysis, and acute renal failure. While it is not known whether this interaction occurs with fibrates other than gemfibrozil, myopathy and rhabdomyolysis have occasionally been associated with the use of other fibrates alone, including clofibrate. Therefore, the combined use of lovastatin with other fibrates should generally be avoided.

Physicians contemplating combined therapy with lovastatin and lipid-lowering doses of nicotinic acid or with immunosuppressive drugs should carefully weigh the potential benefits and risks and should carefully monitor patients for any signs and symptoms of muscle pain, tenderness, or weakness, particularly during the initial months of therapy and during any periods of upward dosage titration of either drug. Periodic creatine phosphokinase (CPK) determinations may be considered in such situations, but there is no assurance that such monitoring will prevent the occurrence of severe myopathy. The monitoring of lovastatin drug and metabolite levels may be considered in transplant patients who are treated with immunosuppressives and lovastatin.

Lovastatin therapy should be temporarily withheld or discontinued in any patient with an acute, serious condition suggestive of a myopathy or having a risk factor predisposing to the development of renal failure secondary to rhabdomyolysis, including: severe acute infection, hypotension, major surgery, trauma, severe metabolic, endocrine, and electrolyte disorders, and uncontrolled seizures.

Myalgia has been associated with lovastatin therapy. Transient, mildly elevated CPK levels are commonly seen in lovastatin-treated patients. However, in early clinical trials, approximately 0.5% of patients developed a myopathy, i.e., myalgia or muscle weakness associated with markedly elevated CPK levels. In the EXCEL study (see CLINICAL PHARMACOLOGY, *Clinical Studies* in the full Prescribing Information), 5 patients (0.1%) taking lovastatin alone (1 at 40 mg q.p.m. and 4 at 40 mg b.i.d.) developed myopathy (muscle symptoms and CPK levels >10 times the upper limit of normal). Myopathy should be considered in any patient with diffuse myalgias, muscle tenderness or weakness, and/or marked elevation of CPK. Patients should be advised to report promptly any unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever. Lovastatin therapy should be discontinued if markedly elevated CPK levels occur or myopathy is diagnosed or suspected.

Most of the patients who have developed myopathy (including rhabdomyolysis) while taking lovastatin were receiving concomitant therapy with immunosuppressive drugs, gemfibrozil, or lipid-lowering doses of nicotinic acid. In clinical trials, about 30% of patients on concomitant immunosuppressive therapy including cyclosporine developed myopathy; the corresponding percentages for gemfibrozil and niacin were approximately 5% and 2%, respectively.

In 6 patients with cardiac transplants taking immunosuppressive therapy including cyclosporine concomitantly with lovastatin 20 mg/day, the average plasma level of active metabolites derived from lovastatin was elevated to approximately 4 times the expected levels. Because of an apparent relationship between increased plasma levels of active metabolites derived from lovastatin and myopathy, the daily dosage in patients taking immunosuppressants should not exceed 20 mg/day (see DOSAGE AND ADMINISTRATION). Even at this dosage, the benefits and risks of using lovastatin in patients taking immunosuppressants should be carefully considered.

PRECAUTIONS: *General:* Before instituting therapy with MEVACOR, an attempt should be made to control hypercholesterolemia with appropriate diet, exercise, and weight reduction in obese patients, and to treat other underlying medical problems (see INDICATIONS AND USAGE in the full Prescribing Information).

Lovastatin may elevate CPK and transaminase levels (see WARNINGS and ADVERSE REACTIONS). This should be considered in the differential diagnosis of chest pain in a patient on therapy with lovastatin.

Homozygous Familial Hypercholesterolemia: MEVACOR is less effective in patients with the rare homozygous familial hypercholesterolemia, possibly because these patients have no functional LDL receptors. MEVACOR appears to be more likely to raise serum transaminases (see ADVERSE REACTIONS) in these homozygous patients.

Information for Patients: Patients should be advised to report promptly any unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever.

Drug Interactions: Immunosuppressive Drugs, Gemfibrozil, Niacin (Nicotinic Acid), Erythromycin: See WARNINGS, *Skeletal Muscle.*

Coumarin Anticoagulants: In a small clinical trial in which lovastatin was administered to warfarin-treated patients, no effect on prothrombin time was detected. However, another HMG-CoA reductase inhibitor has been found to produce a less than 2-second increase in prothrombin time in healthy volunteers receiving low doses of warfarin. Also, bleeding and/or increased prothrombin time have been reported in a few patients taking coumarin anticoagulants concomitantly with lovastatin. It is recommended that in patients taking anticoagulants, prothrombin time be determined before starting lovastatin and frequently enough during early therapy to ensure that no significant alteration of prothrombin time occurs. Once a stable prothrombin time has been documented, prothrombin times can be monitored at the intervals usually recommended for patients on coumarin anticoagulants. If the dose of lovastatin is changed, the same procedure should be repeated. Lovastatin therapy has not been associated with bleeding or with changes in prothrombin time in patients not taking anticoagulants.

Antipyrine: Because lovastatin had no effect on the pharmacokinetics of antipyrine or its metabolites, interactions of other drugs metabolized via the same cytochrome isozymes are not expected.

Propranolol: In normal volunteers, there was no clinically significant pharmacokinetic or pharmacodynamic interaction with concomitant administration of single doses of lovastatin and propranolol.

Digoxin: In patients with hypercholesterolemia, concomitant administration of lovastatin and digoxin resulted in no effect on digoxin plasma concentrations.

Other Concomitant Therapy: Although specific interaction studies were not performed, in clinical studies lovastatin was used concomitantly with beta blockers, calcium channel blockers, diuretics, and nonsteroidal anti-inflammatory drugs (NSAIDs) without evidence of clinically significant adverse interactions.

Endocrine Function: HMG-CoA reductase inhibitors interfere with cholesterol synthesis and as such might theoretically blunt adrenal and/or gonadal steroid production. Results of clinical trials with drugs in this class have been inconsistent with regard to drug effects on basal and reserve steroid levels. However, clinical studies have shown that lovastatin does not reduce basal plasma cortisol concentration or impair adrenal reserve and does not reduce basal plasma testosterone concentration. Another HMG-CoA reductase inhibitor has been shown to reduce the plasma testosterone response to HCG. In the same study, the mean testosterone response to HCG was slightly but not significantly reduced after treatment with lovastatin 40 mg daily for 16 weeks in 21 men. The effects of HMG-CoA reductase inhibitors on male fertility have not been studied in adequate numbers of male patients. The effects, if any, on the pituitary-gonadal axis in premenopausal women are unknown. Patients treated with lovastatin who develop clinical evidence of endocrine dysfunction should be evaluated appropriately. Caution should also be exercised if an HMG-CoA reductase inhibitor or other agent used to lower cholesterol levels is administered to patients also receiving other drugs (e.g., ketoconazole, spironolactone, cimetidine) that may decrease the levels or activity of endogenous steroid hormones.

CNS Toxicity: Lovastatin produced optic nerve degeneration (Wallerian degeneration of retinogeniculate fibers) in clinically normal dogs in a dose-dependent fashion starting at 60 mg/kg/day, a dose that produced mean plasma drug levels about 30 times higher than the mean drug level in humans taking the highest recommended dose (as measured by total enzyme inhibitory activity). Vestibulocochlear Wallerian-like degeneration and retinal ganglion cell chromatolysis were also seen in dogs treated for 14 weeks at 180 mg/kg/day, a dose that resulted in a mean plasma drug level (C_{max}) similar to that seen with the 60 mg/kg/day dose.

CNS vascular lesions, characterized by perivascular hemorrhage and edema, mononuclear cell infiltration of perivascular spaces, perivascular fibrin deposits, and necrosis of small vessels, were seen in dogs treated with lovastatin at a dose of 180 mg/kg/day, a dose that produced plasma drug levels (C_{max}) about 30 times higher than the mean values in humans taking 80 mg/day.

Similar optic nerve and CNS vascular lesions have been observed with other drugs of this class.

Carcinogenesis, Mutagenesis, Impairment of Fertility: In a 21-month carcinogenic study in mice, there was a statistically significant increase in the incidence of hepatocellular carcinomas and adenomas in both males and females at 500 mg/kg/day. This dose produced a total plasma drug exposure 3 to 4 times that of humans given the highest recommended dose of lovastatin (drug exposure was measured as total HMG-CoA reductase inhibitory activity in extracted plasma). Tumor increases were not seen at 20 and 100 mg/kg/day, doses that produced drug exposures of 0.3 to 2 times that of humans at the 80 mg/day dose. A statistically significant increase in pulmonary adenomas was seen in female mice at approximately 4 times the human drug exposure. (Although mice were given 300 times the human dose [HD] on an mg/kg body weight basis, plasma levels of total inhibitory activity were only 4 times higher in mice than in humans given 80 mg of MEVACOR® [Lovastatin].)

There was an increase in incidence of papilloma in the nonglandular mucosa of the stomach of mice beginning at exposures of 1 to 2 times that of humans. The glandular mucosa was not affected. The human stomach contains only glandular mucosa.

In a 24-month carcinogenicity study in rats, there was a positive dose-response relationship for hepatocellular carcinogenicity in males at drug exposures 2 to 7 times that of human exposure at 80 mg/day (doses in rats were 5, 30, and 180 mg/kg/day).

A chemically similar drug in this class was administered to mice for 72 weeks at 25, 100, and 400 mg/kg body weight, which resulted in mean serum drug levels approximately 3, 15, and 33 times higher than the mean human serum drug concentration (as total inhibitory activity) after a 40-mg oral dose. Liver carcinomas were significantly increased in high-dose females and mid- and high-dose males, with a maximum incidence of 90% in males. The incidence of adenomas of the liver was significantly increased in mid- and high-dose females. Drug treatment also significantly increased the incidence of lung adenomas in mid- and high-dose males and females. Adenomas of the Harderian gland (a gland of the eye of rodents) were significantly higher in high-dose mice than in controls.

No evidence of mutagenicity was observed in a microbial mutagen test using mutant strains of *Salmonella typhimurium* with or without rat or mouse liver metabolic activation. In addition, no evidence of damage to genetic material was noted in an *in vitro* alkaline elution assay using rat or mouse hepatocytes, a V-79 mammalian cell forward mutation study, an *in vitro* chromosome aberration study in CHO cells, or an *in vivo* chromosomal aberration assay in mouse bone marrow.

Drug-related testicular atrophy, decreased spermatogenesis, spermatocytic degeneration, and giant cell formation were seen in dogs starting at 20 mg/kg/day. Similar findings were seen with another drug in this class. No drug-related effects on fertility were found in studies with lovastatin in rats. However, in studies with a similar drug in this class, there was decreased fertility in male rats treated for 34 weeks at 25 mg/kg body weight, although this effect was not observed in a subsequent fertility study when this same dose was administered for 11 weeks (the entire cycle of spermatogenesis, including epididymal maturation). In rats treated with this same reductase inhibitor at 180 mg/kg/day, seminiferous tubule degeneration (necrosis and loss of spermatogenic epithelium) was observed. No microscopic changes were observed in the testes from rats of either study. The clinical significance of these findings is unclear.

Pregnancy: Pregnancy Category X: See CONTRAINDICATIONS.

Safety in pregnant women has not been established. Lovastatin has been shown to produce skeletal malformations at plasma levels 40 times the human exposure (for mouse fetus) and 80 times the human exposure (for rat fetus) based on mg/m² surface area (doses were 800 mg/kg/day). No drug-induced changes were seen in either species at multiples of 8 times (rat) or 4 times (mouse) the human exposure based on surface area. No evidence of malformations was noted in rabbits at exposures up to 3 times the human exposure (dose of 15 mg/kg/day, the highest tolerated dose). MEVACOR should be administered to women of childbearing potential only when such patients are highly unlikely to conceive and have been informed of the potential hazards. If the woman becomes pregnant while taking MEVACOR, it should be discontinued, and the patient advised again as to the potential hazards to the fetus.

Nursing Mothers: It is not known whether lovastatin is excreted in human milk. Because a small amount of another drug in this class is excreted in human breast milk and because of the potential for serious adverse reactions in nursing infants, women taking MEVACOR should not nurse their infants (see CONTRAINDICATIONS).

Pediatric Use: Safety and effectiveness in children and adolescents have not been established. Because children and adolescents are not likely to benefit from cholesterol lowering for at least a decade and because experience with this drug is limited (no studies in subjects below the age of 20 years), treatment of children with lovastatin is not recommended at this time.

ADVERSE REACTIONS: MEVACOR® (Lovastatin) is generally well tolerated adverse reactions usually have been mild and transient. Less than 1% o patients were discontinued from controlled clinical studies of up to 14 week due to adverse experiences attributable to MEVACOR. About 3% of patient were discontinued from extensions of these studies due to adverse exper ences attributable to MEVACOR; about half of these patients were discontinue due to increases in serum transaminases. The median duration of therapy i these extensions was 5.2 years.

In the EXCEL study (see CLINICAL PHARMACOLOGY, *Clinical Studies* in th full Prescribing Information), 4.6% of the patients treated up to 48 weeks wer discontinued due to clinical or laboratory adverse experiences that were rate by the investigator as possibly, probably, or definitely related to therapy wit MEVACOR. The value for the placebo group was 2.5%.

Clinical Adverse Experiences: Adverse experiences reported in patients (% treated with MEVACOR (n=613) in controlled clinical studies are *Gastrointestinal:* constipation, 4.9; diarrhea, 5.5; dyspepsia, 3.9; flatus, 6.4 abdominal pain/cramps, 5.7; heartburn, 1.6; nausea, 4.7; *Musculoskeleta* muscle cramps, 1.1; myalgia, 2.4; *Nervous System/Psychiatric:* dizziness, 2.0 headache, 9.3; *Skin:* rash/pruritus, 5.2; *Special Senses:* blurred vision, 1.5 dysgeusia, 0.8.

Laboratory Tests: Marked persistent increases of serum transaminases hav been noted (see WARNINGS).

About 11% of patients had elevations of creatine phosphokinase (CPK levels of at least twice the normal value on one or more occasions. The corre sponding values for the control agents were cholestyramine, 9%, and probu col, 2%. This was attributable to the noncardiac fraction of CPK. Large increase in CPK have sometimes been reported (see WARNINGS, *Skeletal Muscle*).

Expanded Clinical Evaluation of Lovastatin (EXCEL) Study: Clinical Adverse Experiences: MEVACOR was compared to placebo in 8,245 patients wit hypercholesterolemia (total cholesterol 240 to 300 mg/dL [6.2–7.8 mmol/L]) i the randomized, double-blind, parallel, 48-week EXCEL study. Clinical adverse experiences reported as possibly, probably, or definitely drug related in ≥1% o any treatment group are shown in the table below. For no event was the inci dence on drug and placebo statistically different.

		MEVACOR			
	Placebo (n=1,663) %	20 mg q.p.m. (n=1,642) %	40 mg q.p.m. (n=1,645) %	20 mg b.i.d. (n=1,646) %	40 mg b.i.d. (n=1,649) %
Body as a Whole					
Asthenia	1.4	1.7	1.4	1.5	1.2
Gastrointestinal					
Abdominal pain	1.6	2.0	2.0	2.2	2.5
Constipation	1.9	2.0	3.2	3.2	3.5
Diarrhea	2.3	2.6	2.4	2.2	2.6
Dyspepsia	1.9	1.3	1.3	1.0	1.6
Flatulence	4.2	3.7	4.3	3.9	4.5
Nausea	2.5	1.9	2.5	2.2	2.2
Musculoskeletal					
Muscle cramps	0.5	0.6	0.8	1.1	1.0
Myalgia	1.7	2.6	1.8	2.2	3.0
Nervous System/ Psychiatric					
Dizziness	0.7	0.7	1.2	0.5	0.5
Headache	2.7	2.6	2.8	2.1	3.2
Skin					
Rash	0.7	0.8	1.0	1.2	1.3
Special Senses					
Blurred vision	0.8	1.1	0.9	0.9	1.2

Other clinical adverse experiences reported as possibly, probably, or defi nitely drug related in 0.5 to 1% of patients in any drug-treated group are liste below. In all these cases, the incidence on drug and placebo was not statistical ly different. *Body as a Whole:* chest pain; *Gastrointestinal:* acid regurgitation dry mouth; vomiting; *Musculoskeletal:* leg pain, shoulder pain, arthralgia *Nervous System/Psychiatric:* insomnia, paresthesia; *Skin:* alopecia, pruritus *Special Senses:* eye irritation.

Concomitant Therapy: In controlled clinical studies in which lovastatin wa administered concomitantly with cholestyramine, no adverse reactions peculi to this concomitant treatment were observed. The adverse reactions tha occurred were limited to those reported previously with lovastati or cholestyramine. Other lipid-lowering agents were not administered cor comitantly with lovastatin during controlled clinical studies. Preliminary dat suggest that the addition of either probucol or gemfibrozil to therapy wit lovastatin is not associated with greater reduction in LDL cholesterol than tha achieved with lovastatin alone. In uncontrolled clinical studies, most of th patients who have developed myopathy were receiving concomitant therap with immunosuppressive drugs, gemfibrozil, or niacin (nicotinic acid) (se WARNINGS, *Skeletal Muscle*).

The following effects have been reported with drugs in this class:

Skeletal: myopathy, rhabdomyolysis, arthralgias.

Neurological: dysfunction of certain cranial nerves (including alteration o taste, impairment of extraocular movement, facial paresis), tremor, vertigo memory loss, paresthesia, peripheral neuropathy, peripheral nerve palsy, anx ety, insomnia, depression.

Hypersensitivity Reactions: an apparent hypersensitivity syndrome has bee reported rarely that has included one or more of the following features: ana phylaxis, angioedema, lupus erythematous-like syndrome, polymyalgi rheumatica, vasculitis, purpura, thrombocytopenia, leukopenia, hemolytic ane mia, positive ANA, ESR increase, arthritis, arthralgia, urticaria, asthenia, photo sensitivity, fever, chills, flushing, malaise, dyspnea, toxic epidermal necrolysis erythema multiforme, including Stevens-Johnson syndrome.

Gastrointestinal: pancreatitis, hepatitis, including chronic active hepatitis cholestatic jaundice, fatty change in liver; and rarely, cirrhosis, fulminant hep atic necrosis, and hepatoma; anorexia, vomiting.

Skin: alopecia.

Reproductive: gynecomastia, loss of libido, erectile dysfunction.

Eye: progression of cataracts (lens opacities), ophthalmoplegia.

Laboratory Abnormalities: elevated transaminases, alkaline phosphatase, an bilirubin; thyroid function abnormalities.

OVERDOSAGE: After oral administration of MEVACOR to mice, the media lethal dose observed was >15 g/m².

Five healthy human volunteers have received up to 200 mg of lovastatin a single dose without clinically significant adverse experiences. A few cases accidental overdosage have been reported; no patients had any specific symp toms, and all patients recovered without sequelae. The maximum dose take was 5 to 6 g.

Until further experience is obtained, no specific treatment of overdosag with MEVACOR can be recommended.

The dialyzability of lovastatin and its metabolites in man is not known at present

DOSAGE AND ADMINISTRATION: The patient should be placed on a standar cholesterol-lowering diet before receiving MEVACOR and should continue o this diet during treatment with MEVACOR. MEVACOR should be given with meals

The recommended starting dose is 20 mg once a day given with the evenin meal. The recommended dosing range is 20 to 80 mg/day in single or divide doses; the maximum recommended dose is 80 mg/day. Adjustments of dosag should be made at intervals of 4 weeks or more. Doses should be individua ized according to the patient's response (see Tables I to IV under CLINICA PHARMACOLOGY, *Clinical Studies* in the full Prescribing Information for dose response results).

In patients taking immunosuppressive drugs concomitantly with lovastati (see WARNINGS, *Skeletal Muscle*), therapy should begin with 10 mg MEVACOR and should not exceed 20 mg/day.

Cholesterol levels should be monitored periodically, and considerati should be given to reducing the dosage of MEVACOR if cholesterol levels fa below the targeted range.

Dosage in Patients with Renal Insufficiency: In patients with severe renal insu ficiency (creatinine clearance <30 mL/min), dosage increases above 20 mg/da should be carefully considered and, if deemed necessary, implemented ca tiously (see CLINICAL PHARMACOLOGY in the full Prescribing Information an WARNINGS, *Skeletal Muscle*).

For more detailed information, consult your MSD Representative or see th Prescribing Information.

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J1MC56(519

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Angiographic Findings in the Coronary Arteries After Thrombolysis in Acute Myocardial Infarction

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The angiographic appearance of the coronary arteries was examined in 308 patients with acute myocardial infarction (AMI) who received high-dose intravenous thrombolytic therapy. Coronary angiography was performed on day 7 after admission to the hospital. Patients had an average of 2.4 discrete arterial narrowings or obstructions. The narrowings were proximal and related to bifurcations. Four fifths of the culprit arteries were patent; 104 (34%) had a ruptured plaque, 22 (7%) had an ulcerated plaque, and in 190 (62%) the lesions were eccentric. Patients differed from a comparable, previously studied, control series of 302 patients with chronic stable angina pectoris who had more extensive disease. They had 5.7 narrowings/patient, also located proximally and at bifurcations, but more widely distributed in the coronary tree. Patients with AMI who are suitable for thrombolysis have a unique coronary angiographic picture. The data confirm that AMI is caused by sudden rupture of a localized atheromatous plaque that initiates an obstructive thrombotic cascade.

(Am J Cardiol 1992;70:715–723)

Acute myocardial infarction (AMI) is usually due to sudden thrombotic obstruction of a major coronary artery.[1] Pathologic,[2–5] angiographic[6–9] and angioscopic[10] studies have shown 6 pathogenetic processes: (1) insidious accretion of atheromatous plaques, (2) sudden plaque rupture, (3) thrombus formation, (4) spontaneous fibrinolysis, (5) rethrombosis, and (6) arterial spasm or endothelial dysfunction.

Coronary angiography in AMI showed an 87% occlusion rate in patients studied within 4 hours after symptom onset. Spontaneous fibrinolysis occurs, so that occlusion is present in 65% of patients after 12 to 24 hours, and in 21% two weeks later.[1,11]

We examined the coronary angiographic appearance of the coronary lesions in 308 patients with AMI who were studied 6 to 8 days after high-dose intravenous thrombolytic treatment with streptokinase.[12–15] The results were then compared with those of a previous study that examined the distribution of coronary lesions in 302 patients with stable angina pectoris.[16] This study compares the extent, distribution and nature of the angiographic lesions in the 2 groups of patients.

METHODS

Three hundred eight consecutive patients with AMI who were treated with intravenous streptokinase underwent coronary angiography 7 days (range 6 to 8) after the acute event. This group represents 30% of our hospital population for AMI. No patient underwent emergent angiography. Patients receiving thrombolysis with ≥30 minutes but ≤4 hours of continuous, typical, myocardial ischemic chest pain unresponsive to sublingual isosorbide dinitrate or nifedipine were selected for the study. New ST-segment elevation and reciprocal changes were also required for inclusion. Exclusion criteria were age >70 years, history of severe hypertension (>200/110 mm Hg), peptic ulcer, cerebrovascular accident, recent surgery and bleeding tendency. Patients received 1.5 million units of streptokinase as an intravenous infusion over 1 hour. Aspirin and intravenous heparin therapy were begun immediately.

Coronary angiography was performed 7 days (range 6 to 8) after the acute event, using the Judkins technique. At least 6 views of the left coronary system (including craniocaudal positions) and ≥3 views of the right coronary system were filmed using a high-resolution, magnifying, 4.5 inch, General Electric image intensifier. Left ventriculography was performed in the right anterior oblique position, and left ventricular function was estimated quantitatively.[15]

From the Cardiac Department, Hadassah University Hospital, Jerusalem, Israel. This study was supported by a grant from the Israeli-German Binational Research Foundation, Jerusalem, Israel. Manuscript received January 22, 1992; revised manuscript received and accepted May 27, 1992.

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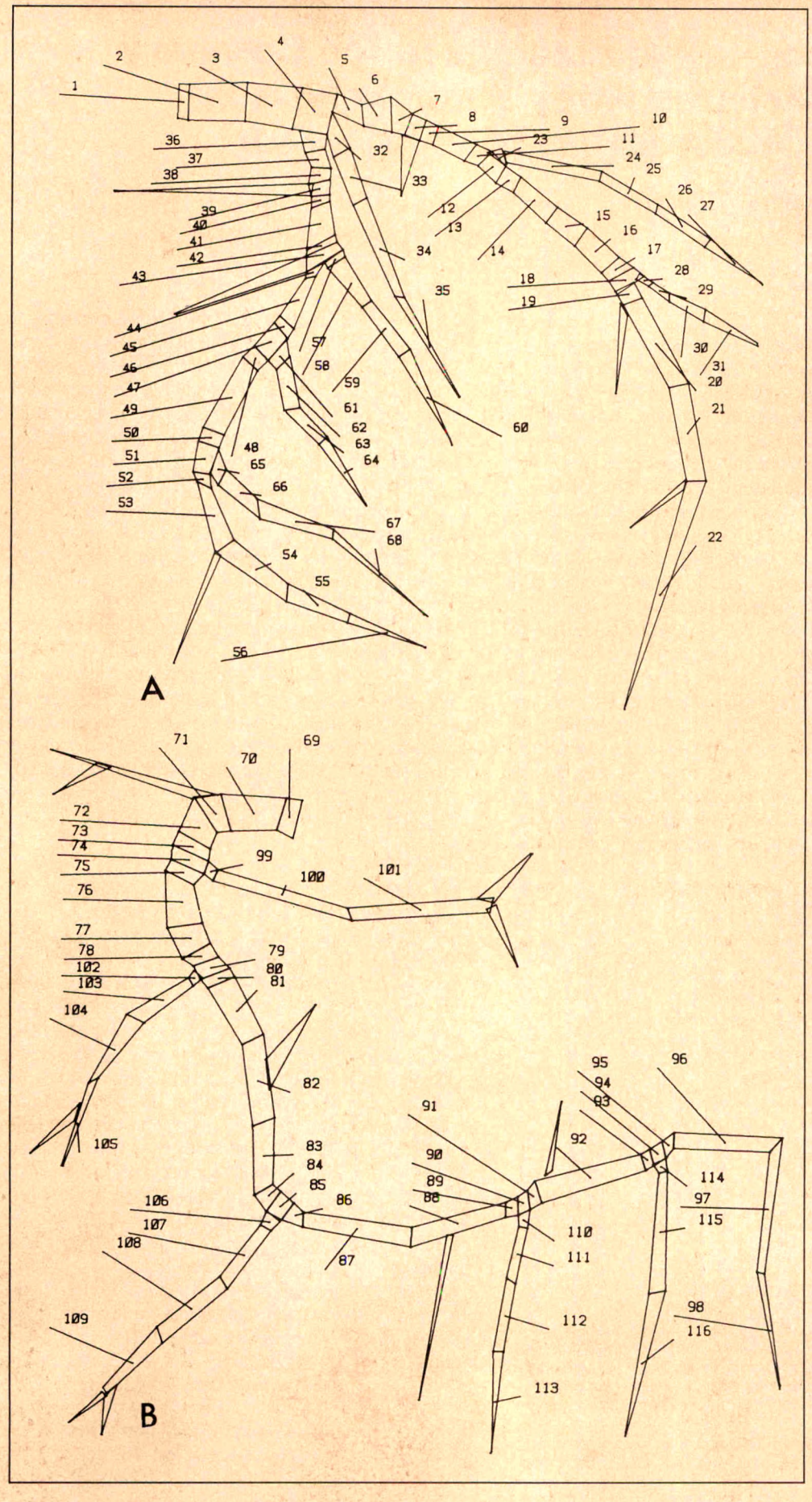


FIGURE 1. A 116-segment anatomic model of coronary artery tree. *A*, left coronary artery. *B*, right coronary artery. Reproduced by permission.[16]

The coronary angiogram was examined by 2 different observers. The following parameters were noted:

1. Site of each lesion using a detailed 116-segment model that takes into account the origins and points of branching of the vessels. To allow precise localization of the narrowing in or adjacent to the origins of major vessels or branches and to differentiate narrowing directly opposite points of branching and immediately proximal and distal to these points, we included exceptionally short segments in the model at these sites. Each short segment was taken to be 2 mm long (Figure 1).[17]

2. Severity of the stenosis was measured manually using a high-magnification projector and mechanical calipers. Percent stenosis was calculated by estimating the stenosis in the projection that showed the greatest narrowing. The nearest normal segment was used for comparison; this overestimates the severity of eccentric stenosis. Both the lesion responsible for the infarct (culprit) and all other significant atheromatous plaques were reviewed. The narrowing was measured to avoid angulation and overlapping from adjacent branches. We did not use a computerized electronic caliper or densitometric analysis. All visible lesions were recorded, but lesions with >50% narrowing were regarded as significant. Interobserver variability was <10%.

3. The morphology of each lesion was estimated in relation to the following: (A) concentricity (circumferential lesion) or eccentricity, (B) ulceration (presence of clear protrusion of contrast medium in region of narrowing), (C) presence of a ruptured plaque (with obvious dissection or signs of endothelial discontinuity), and (D) presence of fresh thrombus (clear protruding filling defect, pedunculated or sessile).[7,8,18–21]

4. The presence of collateral vessels.[22]

The position of each lesion was localized on the coronary arteriogram and recorded on the computer-generated coronary model[16,17] (Figure 1).

The culprit lesion was regarded as the lesion related to the electrocardiographically documented infarct site.

RESULTS

Demographic data: Coronary angiograms were analyzed in 308 consecutive patients (260 men [84%] and 48 women [16%], mean age 56 ± 10 years). Two hundred fifty-nine patients (84%) had a first infarct, and 49 (16%) had history of a previous infarct. In 155 patients (50%) the infarct was anterior, in 151 (49%) it was inferior, and other sites accounted for the remainder. Duration of pain from onset to administration of streptokinase was 1.8 ± 0.9 hour.

Coronary artery anatomy: SEVERITY, LOCATION AND EXTENT OF CORONARY LESIONS: The extent and distribution of all lesions in each artery are shown in Figure 2. The number of lesions in each patient are shown in Figure 3. Patients had a mean of 2.4 lesions that were localized (<5 mm long).

In 241 patients (78%), the culprit artery was patent; 64 (27%) had >90% diameter narrowing, 86 (36%) had 75 to 90% narrowing, 80 (33%) had 50 to 75% narrowing, and 11 (5%) had <50% narrowing. Most culprit lesions were localized at bifurcations; 77 were localized immediately proximal to, 70 at and 93 after a bifurcation, and 68 were unrelated to bifurcations. Lesions in the left anterior descending artery were related to either the origin of the artery or the first perforating branch, or near the origin of the first diagonal artery. In the circumflex territory, lesions were more widely distributed, but again were proximal and related to the origin of the atrial or marginal arteries. Similarly, in the right coronary artery, lesions were proximal and related to bifurcations and branches.

MORPHOLOGY OF THE CULPRIT LESION: Concentric lesions were present in 118 patients (38%) and eccentric lesions in 190 (62%) (Figure 4).

Sixty-seven patients (22%) had total occlusion of the artery (Figure 5). One hundred four patients (34%) had evidence of a ruptured plaque, and in 22 (7%) the plaque was ulcerated (Figure 6). Fifty-seven patients (19%) had fresh thrombus (32 in relation to a ruptured plaque, and 3 on an ulcer).

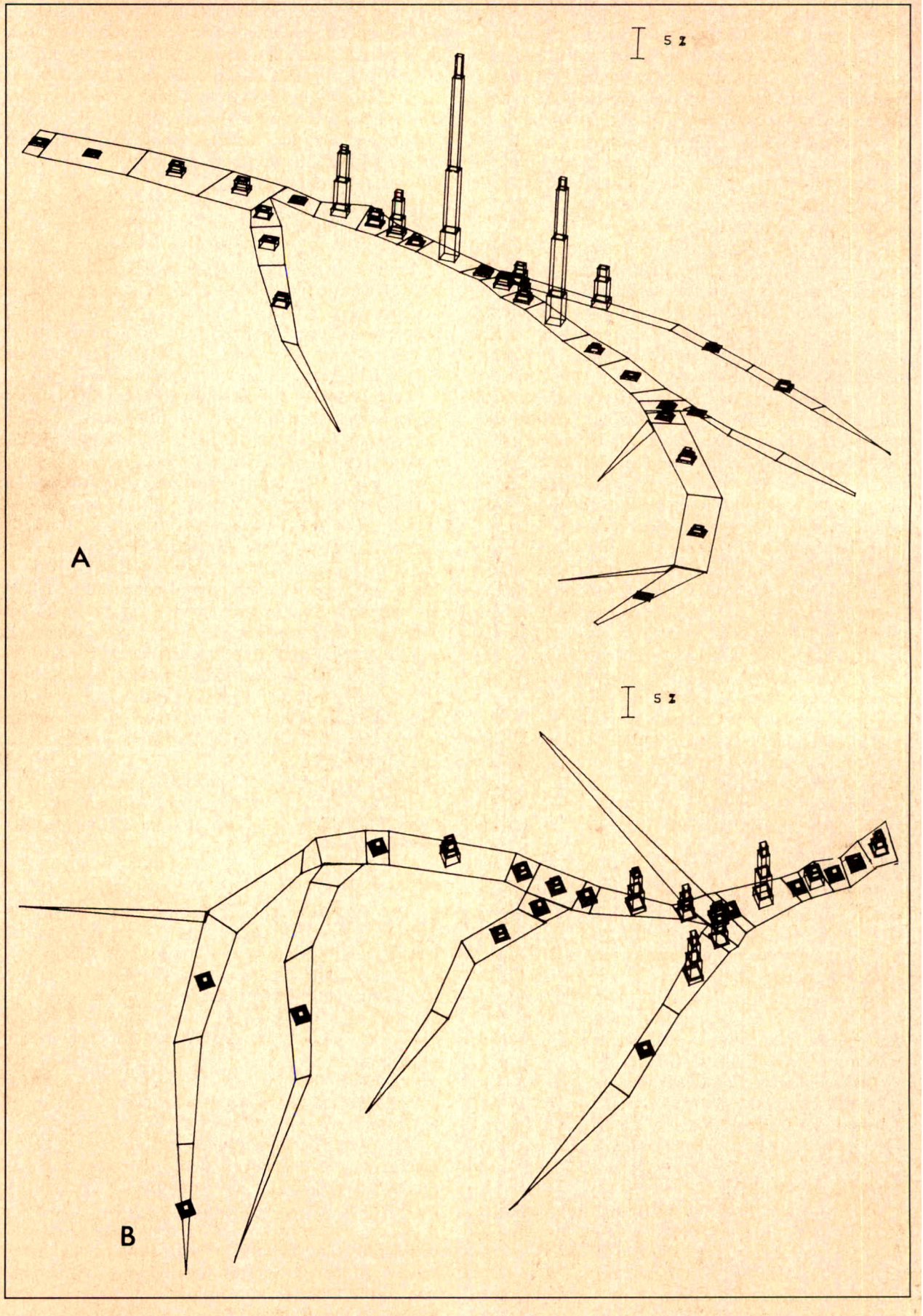
Comparison to patients with chronic stable angina pectoris: In a previous study, we examined 302 consecutive patients (232 men [77%] and 70 women [23%], average age 55 years, range 27 to 74) with coronary artery disease who underwent coronary angiography for stable angina pectoris (Figure 7).[16] In 181 patients (60%), ≥1 of 7 left ventricular regions contracted abnormally, indicating previous AMI. These patients had more disseminated coronary arterial lesions. Patients had a mean of 5.7 lesions, more frequent in the proximal portions of the 3 major arteries. Lesions were often adjacent to branch points. The prevalence of lesions was greater in the 2 mm segment immediately distal to the points of branching than directly at the branch. Narrowing in the left main coronary artery was more frequent in its distal half. Mild, moderate and severe narrowing were distributed in the same ratio in each region of the coronary tree.

Thus, the lesions were proximal, and related to bifurcations and curves in the artery, but were more extensive, and the angiograms showed disseminated disease.

DISCUSSION

This study examined a specific group of patients with AMI who fulfilled the current criteria for thrombolytic therapy. They were young patients, usually with a first AMI, similar to patients in the First Thrombolysis and Angioplasty in Myocardial Infarction (TAMI I) and the First Thrombolysis in Myocardial Infarction (TIMI I) studies.[23–26] The series did not include patients aged >75 years who were usually admitted with a second or third infarct. In our specific subset of patients, the disease was localized with a mean of 2.4 lesions/patient.

Most patients with a first AMI are asymptomatic before the event, and the preinfarct culprit lesion is probably insignificant.[6,7,27–28] The plaque becomes unstable or vulnerable and ruptures or bursts.[29] This is due to either sudden swelling of the soft fatty lesion with degeneration or fracture of the endothelium. Stress fracture of the endothelium usually occurs at the junction of the atheromatous plaque with normal arterial wall or at the tip of the plaque, and may be a conse-


5 %
A
5 %
B

quence of medial spasm or damage to the endothelium.[30,31] Alternatively, a weak point in the endothelium, absence of underlying collagen support, macrophage infiltration with the secretion of enzymes and other metabolites that facilitate tissue lysis, or hemorrhage into the atheromatous plaque may be the provocative factors.[5] Loss of endothelial continuity exposes underlying collagen, and van Willebrand factor is released. This causes platelet activation and adhesion, and initiates the thrombotic cascade.[1,3,5] A thrombus forms. Spontane-

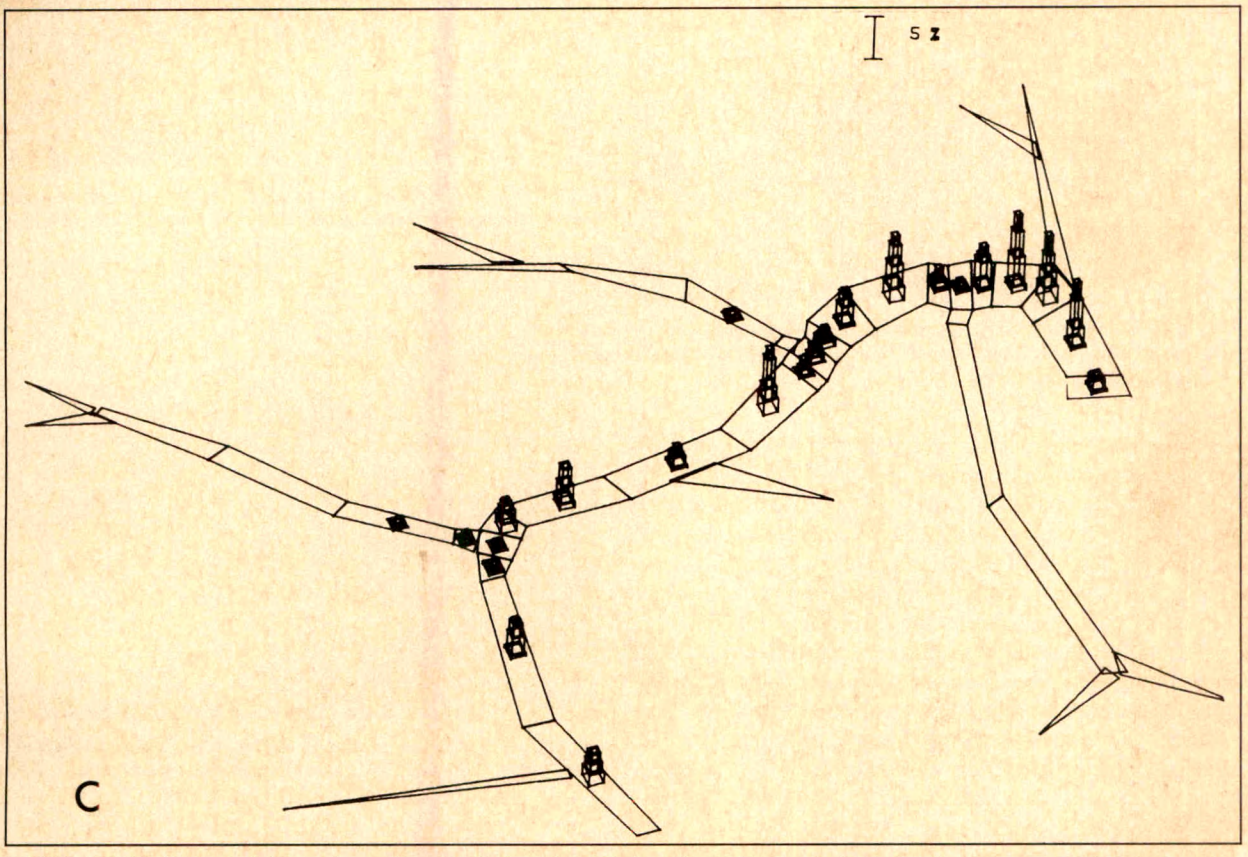


FIGURE 2. Distribution of site and severity of all lesions in patients with acute myocardial infarction who received high-dose intravenous thrombolysis and were studied by coronary angiography 7 days after acute event. *A*, left anterior descending coronary artery showing perforating branches on *left* and diagonal branches on *right*. *B*, left circumflex artery with marginal arteries pointing forward. *C*, right coronary artery (excluding posterior interventricular branch). Incidence of lesions in each segment is shown as 3-dimensional histogram that is subdivided into 4 regions according to severity of narrowing. Each histogram represents narrowing from base upward of <50, 50 to 70, 71 to 99, and 100%, respectively. Disease is located mainly proximally and at bifurcations. The 5% bar is a scale representing 5% of number of patients.

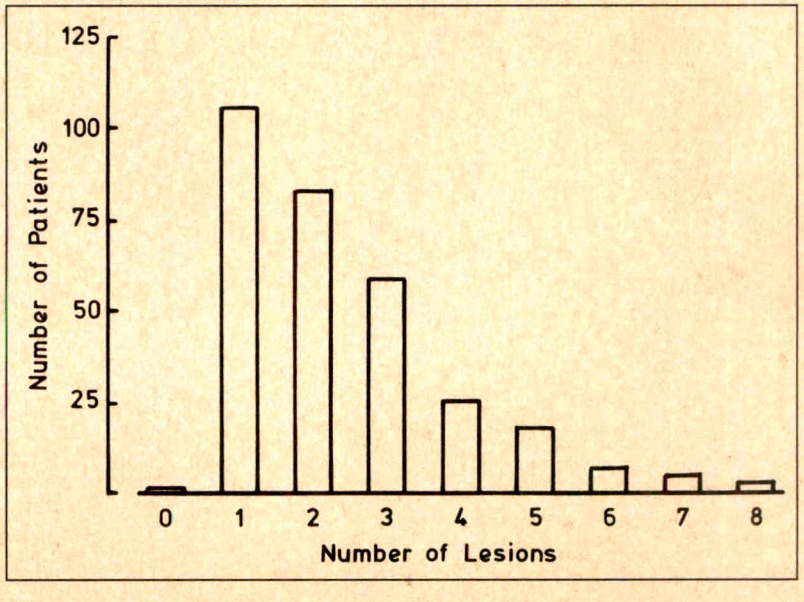


FIGURE 3. Distribution of total number of lesions/patient 7 days after intravenous thrombolytic therapy.

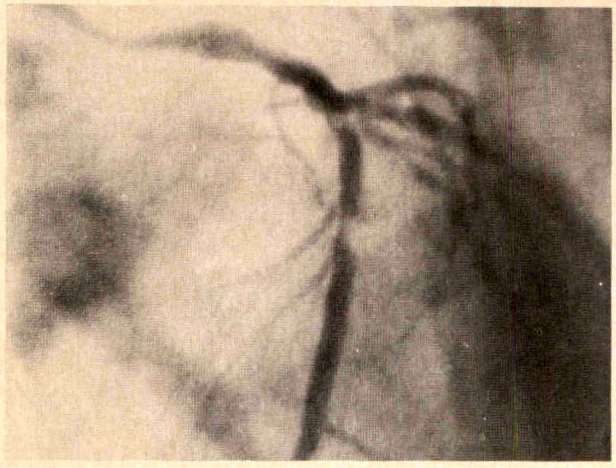


FIGURE 4. Eccentric plaque in left anterior descending coronary artery between 2 perforating branches (craniocaudal left anterior oblique projection).

ous thrombolysis follows, so that there is a dynamic interaction between thrombosis and lysis.[32] The initial lesion partially obstructs flow and promotes stasis and thrombosis; there is then a further interplay between flow and stasis, until either the artery is completely occluded or flow is restored. The superimposed thrombus occluding the artery is responsible for the infarct.

The thrombus then propagates in the area of stagnant flow from the site of obstruction to the next proximal bifurcation where flow continues down the side branch.[3] Spontaneous thrombolysis is frequent.[27] Reocclusion occurs in another 10% of cases.[33,34]

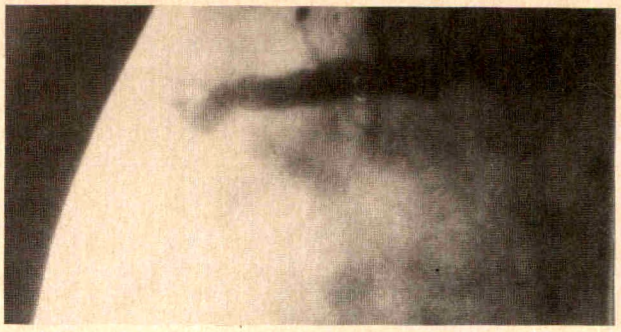


FIGURE 5. Total obstruction of right coronary artery by propagated thrombus. Note abrupt "cut-off" of arterial lumen.

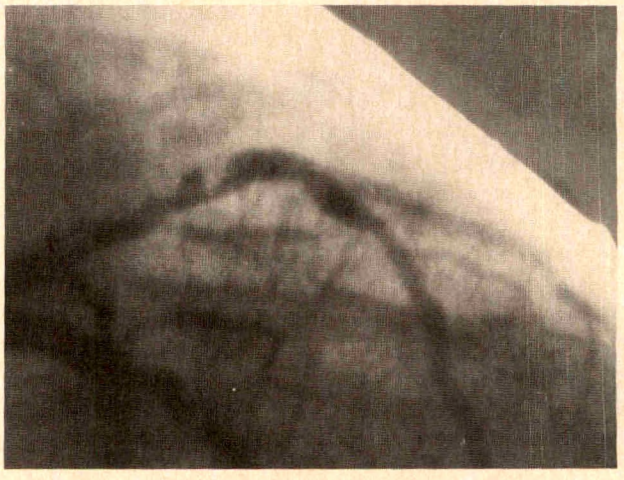
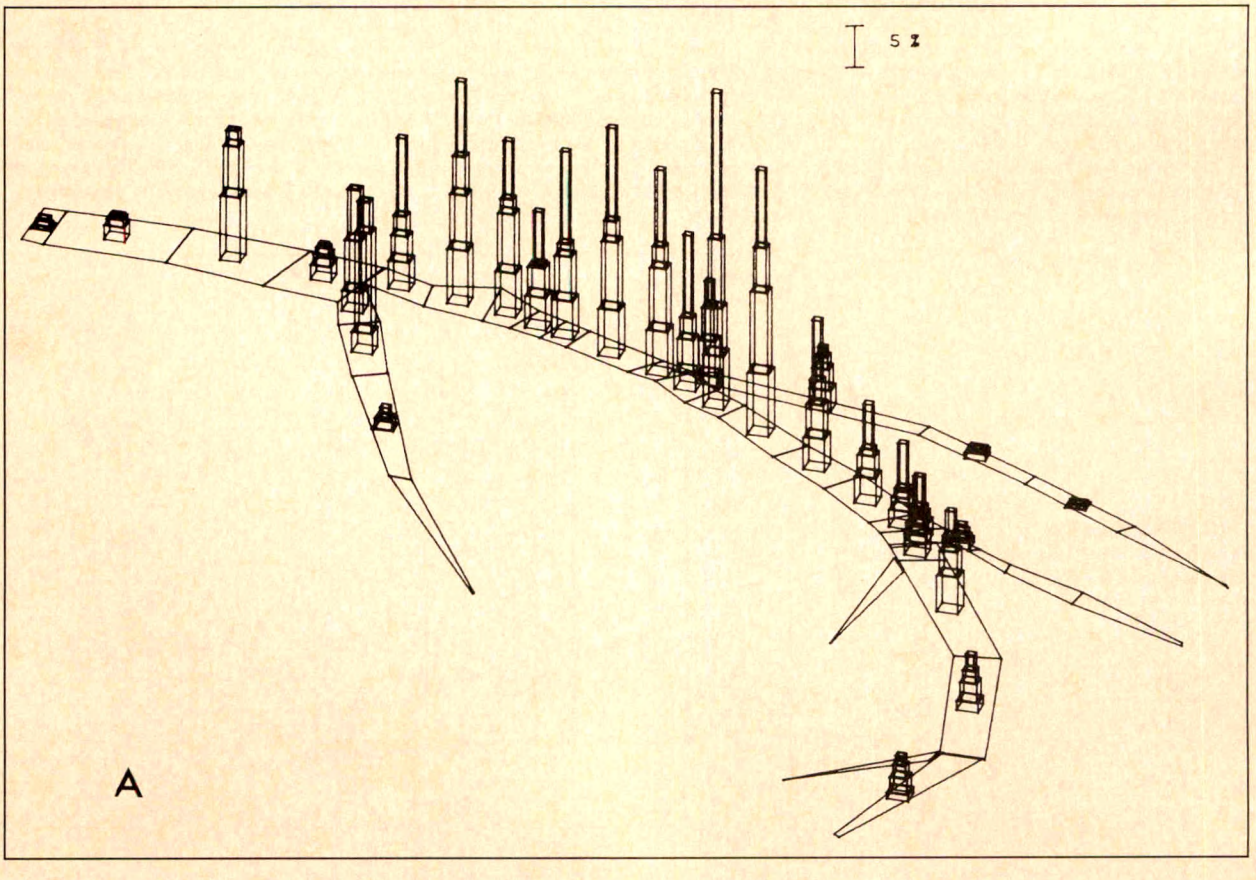


FIGURE 6. Ulcerated plaque in left anterior descending coronary artery (left anterior descending oblique position).



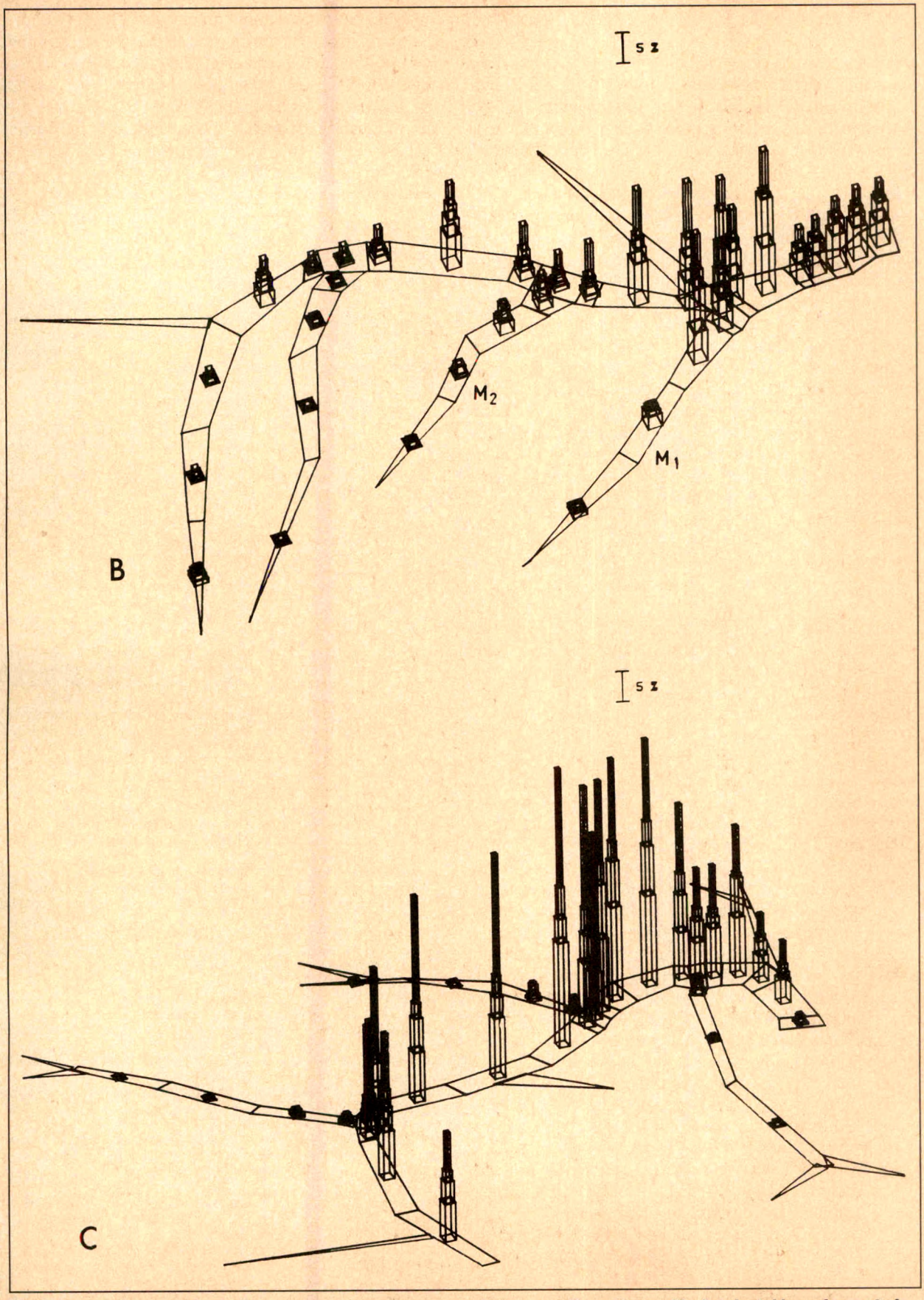


FIGURE 7. Comparative distribution of coronary artery lesions in 302 consecutive patients with chronic stable angina pectoris (compared with Figure 2). *A*, left anterior descending coronary artery. *B*, left circumflex coronary artery. *C*, right coronary artery. Reproduced by permission.[16]

This angiographic study shows that complete obstruction was still present in 22% of cases; thrombus had been successfully lysed in 78%.[14,15] Only a few cases had minimal residual lesions.

In our patients with successful thrombolysis, 190 had an eccentric lesion due to a localized eccentric atheromatous plaque with or without additional, laminated, residual thrombus, 104 had evidence of a ruptured plaque, and 22 had a clearly ulcerated plaque.

Brown et al[6] showed that mild to moderate atherosclerotic coronary artery lesions develop acute thrombotic occlusions and that intracoronary streptokinase partially digests the obstructing thrombus.[6] Patients with concentric lesions had undergone reperfusion; it is probable that persistent clot (either unlysed or reformed) coated the arterial wall, leaving only a residual channel whose form and shape was determined by local rheologic flow factors. The ruptured or ulcerated plaque reflects the underlying atheromatous pathology.[35] Fibrinolytic therapy has little effect on platelet-rich clot.

Our selected subset of patients with AMI presented in an early phase of development of the atherosclerotic disease process when the disease was localized in 1 or 2 sites. If atheroma was present in the other arteries, it was often insignificant and not seen by angiography. One hundred six patients had only 1 atheromatous lesion. It is possible that plaque rupture occurred randomly at other sites; thrombosis did not obstruct the artery or was washed away, and endothelial healing occurred.[5,32] Obstructive culprit lesions were not present in the smaller or distal diagonal or marginal arteries, or in the distal major arteries. It is probable that when these patients rupture their atheromatous plaques, the transmural infarct does not cause classic ST-segment elevation; thus, they were not included in our subset of patients who received thrombolytic therapy.

Localization of the lesions at bifurcations may reflect their pathogenetic mechanisms. Circulating monocytes and cholesterol migrate into the arterial wall at bifurcations where the flow pattern acts as a flow divider, and the cells adhere and are not washed away. Atheroma occurs at these sites. After plaque rupture, thrombus forms, and the low shear stress probably determines why the clot is not detached and progresses to complete occlusion.[36] The subset of patients with AMI differs significantly from that with stable angina pectoris. The latter group had more disseminated disease, with 5.7 lesions/patient. Their lesions were also proximal and related to bifurcations and curvatures, but they were more extensively distributed and probably represented a later stage in the natural history of the disease.[16] After an initial lesion forms, this leads to downstream turbulence and creates a new pattern or flow adjacent to or beyond the initial atheromatous plaque. Thus, the initial isolated lesion causes a series of propagated plaques, and the disease progresses.

Coronary artery atheroma occurs proximally in the major coronary arteries, usually in relation to bifurcations. Abnormal flow shear and stress appear to be the most important initial predisposing factors. Lesions spread in the coronary arteries as the process progresses. Atheromatous plaques appear to be classifiable into the following 2 distinct groups: stable plaques, in which lipid accumulates slowly with time so that progress is slow; and unstable, active or vulnerable plaques that may be small and insignificant initially, but when the arterial wall absorbs cholesterol rapidly or the endothelium ruptures, the thrombotic cascade is initiated, and plaque size changes abruptly. The development of an arterial occlusion that initiates the acute myocardial infarct is therefore an unexpected acute anatomic accident.

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Effect of Beta-Adrenoceptor Blockade on Dipyridamole-Induced Myocardial Asynergies in Coronary Artery Disease

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Twenty-one patients with angiographic evidence of significant coronary artery disease, and positive dypiridamole echocardiographic test results at basal condition and after 7 days of placebo treatment were prospectively studied to see whether β blockade modifies the effects of dipyridamole echocardiographic testing on regional myocardial contractility. Patients were randomized to propranolol (120 mg/day) or placebo treatment in 3 divided doses for 7 days, after which each patient crossed over to the alternate regimen. Dipyridamole-ecocardiographic testing was repeated at the end of each treatment. Propranolol abolished new mechanical signs of transient dipyridamole-induced ischemia (new wall motion abnormalities or an increase in degree of basal asynergies, or both) in 13 of 21 patients. The remaining 8 patients had positive results on dipyridamole echocardiographic testing after the propranolol treatment period.

At basal conditions both heart rate and rate-pressure product were significantly reduced with propanolol; there was also a significant decrease in these parameters at peak dipyridamole infusion. At peak dipyridamole infusion heart rate and rate-pressure product were significantly lower in patients with negative than in those with positive echocardiographic test results after propanolol. Our data show that administration of β blockade significantly reduces the development of transient dipyridamole-induced myocardial asynergies, the earliest markers of acute myocardial ischemia, detected with 2-dimensional echocardiography.

(Am J Cardiol 1992;70:724–727)

Dipyridamole has been used in assessing coronary artery disease in combination with thallium-201,[1,2] radionuclide angiography[3] or 2-dimensional echocardiography.[4,5] This last technique can identify transient wall motion abnormalities, the earliest markers of acute myocardial ischemia induced by dipyridamole infusion, with high sensitivity and specificity. Picano et al[6] demonstrated that high-dose dipyridamole echocardiography in patients with effort angina pectoris and good baseline echocardiograms has a higher specificity and a similar sensitivity than exercise electrocardiography testing. However, antianginal therapy could modify the sensitivity of the test. Kawashima et al[7] demonstrated that antianginal therapy (nitrates or diltiazem) can suppress dipyridamole-induced electrocardiographic changes, and recently, antianginal drugs (β blockers, calcium antagonists and nitrates, alone or in various combination) have been shown to decrease the sensitivity of the dipyridamole echocardiographic test.[8] Few prospective studies are available on the effects of β blocking drugs on dipyridamole-induced asynergies in men. We evaluated the effect of pretreatment with the β-blocking agent propranolol on dipyridamole-induced transient wall motion abnormalities to see whether β blockade modifies the effects of the pharmacologic stress test on regional myocardial contractility.

METHODS

We prospectively studied 23 patients (19 men and 4 women; mean age 61 ± 6 years) with angiographic evidence of significant coronary artery disease, positive dipyridamole echocardiography test results at basal condition and an adequate echocardiographic window. Dipyridamole echocardiography testing was repeated in all 23 patients the day after the first examination to establish the reproducibility of the test. Twenty-one of them had a second positive dipyridamole echocardiography test result (reproducibility 91%), and only these subjects were admitted to the study. Patients with valvular heart disease, congestive heart failure, atrioventricular conduction defects, cardiomyopathy or severe ventricular arrhythmias were excluded from the study.

Patients were randomized to propranolol (120 mg/day) or placebo treatments, given in 3 divided doses daily for 7 days, at the end of which time each patient crossed over to the alternate regimen. Dipyridamole echocardiographic testing was repeated at the end of each treatment period.

Calcium antagonists, nitrates and angiotensin-converting enzyme inhibitors had been discontinued ≥7

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days before dipyridamole testing and were not given throughout the study period. β-adrenergic blocking drugs had been discontinued ≥7 days before dipyridamole testing, and were not given at basal condition or during placebo treatment. Patients drank no coffee or tea for ≥3 hours before the dipyridamole echocardiographic test.

Dipyridamole echocardiography: Dipyridamole was infused through a 21 gauge butterfly needle inserted into a large anterocubital vein at a rate of 0.56 mg/kg body weight over 4 minutes, followed by a 4-minute pause and then 0.28 mg/kg over 2 minutes. The cumulative dose was therefore 0.84 mg/kg over 10 minutes. Twelve-lead electrocardiograms and blood pressure measurements were obtained at baseline and at 1-minute intervals during the first 15 minutes of the study and at 20, 25 and 30 minutes.

Parenteral aminophylline (240 mg) and nitroglycerin were available to reverse significant dipyridamole side effects. The following adverse effects were considered significant: chest pain, dyspnea, ST-segment depression >1 mV, and appearance of myocardial asynergies detected by echocardiography. Aminophylline was administered when 1 or a combination of these events occurred. The electrocardiographic criteria for a positive test result were: horizontal or downsloping ST-segment depression of ≥0.1 mV occurring at the J point and lasting >80 ms. Real-time echocardiographic examination was performed with the patient in a 30° to 60° left lateral decubitus position before, during and after dipyridamole infusion using a wide-angle (105°), phased-array imaging system (Toshiba SSH40A; 3.5 MHz transducer). Images were obtained from the standard parasternal and apical transducer positions. Particular attention was given to the apical 4- and 2-chamber views and the parasternal short-axis plane. For the purpose of analysis, the left ventricle was divided into 4 segments (anterior, septal, lateral and posteroinferior). The motion patterns of the individual segments were described as normal, hypokinetic (reduction of ≥50% in the systolic thickening), akinetic (absence of systolic thickening), dyskinetic (paradoxical systolic movement) and hyperkinetic (exalted kinetics). Evaluation was based on the subjective impression of the inward motion of the endocardial echo toward the center of the left ventricle and on the degree of myocardium thickening. The appearance of new wall motion abnormalities or an increase in basal asynergies, or both, were considered a valid criterion for a positive echocardiographic test result. The mechanical sign of myocardial ischemia previously cited, isolated or associated with clinical and electrocardiographic (ST depression) manifestations, was considered as criterion for stopping the test. The images were displayed in real time at a rate of 58 frames/s and were recorded by means of 0.25 inch (0.64 cm) VHS tape cassette recorder. The initial echocardiographic examination was performed to record baseline images, to explore the cardiac windows, and to establish the transducer positions from which optimal images could be obtained. The transducer positions and echocardiographic planes established during the baseline examination facilitated rapid and optimal studies. The echocardiograms at basal condition and during dipyridamole testing were graded independently by 2 observers unaware of treatment type (placebo or propranolol). In case of disagreement a third observer reviewed the tracings and majority judgment was binding.

Coronary arteriography: Coronary arteriography was conducted by the Sones technique the morning after an overnight fast. Intramuscular diazepam (10 mg) was administered 30 minutes before the study. Selective coronary arteriography was performed in the standard projections and was analyzed for the quantitative evaluation of stenosis severity. For each coronary artery, the frame showing the most significant percent narrowing, in any projection, over the length of that artery was selected and enlarged 10 times. The diameter of the stenosis and that of the most nearly "normal" proximal or distal segments were measured with a digital caliper. The ratio of the 2 measurements was taken as the percent narrowing of that artery. For each vessel, the projection selected for this evaluation was agreed on by 3 experienced angiographers.

Significant coronary artery disease was defined as ≥70% luminal diameter of 1 or more of the major coronary arteries.

Statistical analysis: Statistical analysis was performed by the Fisher exact test as appropriate. Hemodynamic changes induced by dipyridamole administration were analyzed by the Duncan test or by the *t* unpaired test. Values were expressed as mean ± standard deviation, and p values ≤0.05 were considered significant.

RESULTS

Dipyridamole test: echocardiographic and hemodynamic findings: Echocardiographic and hemodynamic findings of the 21 patients during dipyridamole infusion before placebo or propranolol administration are listed in Table I.

In 13 patients the dipyridamole echocardiographic test after propranolol treatment was negative (group 1). In 8 patients the dipyridamole echocardiography test after propranolol was positive (group 2) (propranolol vs placebo $p < 0.001$).

At basal condition, propranolol administration significantly reduced heart rate from 73 ± 13 to 58 ± 11 beats/min ($p < 0.001$) and rate-pressure product from 9.95 ± 2.2 to 7.96 ± 2.3 U × 10^{-3} ($p < 0.001$). At peak of dipyridamole infusion, heart rate decreased from 94 ± 14 to 74 ± 13 beats/min ($p < 0.001$) and rate-pressure product from 13.76 ± 3 to 10.41 ± 3.4 U × 10^{-3} ($p < 0.001$) (Table II).

At peak of dipyridamole infusion, heart rate was significantly lower ($p < 0.02$) in group 1 (69 ± 12 beats/min) than in group 2 (81 ± 11 beats/min); rate-pressure product was also significantly lower ($p < 0.005$) in group 1 (9.02 ± 2.81 U × 10^{-3}) than in group 2 (12.79 ± 3.22 U × 10^{-3}) (Table III).

DISCUSSION

Our data show that β-adrenoceptor blockade significantly reduces the development of transient dipyridamole-induced myocardial asynergies, the earliest mark-

TABLE I Hemodynamic Findings at Basal Condition and at Peak Dipyridamole Infusion Before Placebo or Propranolol Administration

	Basal	Peak	p Value
HR (beats/min)	73 ± 9	96 ± 15	<0.001
SBP (mm HG)	138 ± 14	145 ± 20	NS
DBP (mm HG)	88 ± 9	86 ± 14	NS
RPP ($Ux10^{-3}$)	10.07 ± 1.6	13.92 ± 2.7	<0.001

Values are mean ± SD.
DBP = diastolic blood pressure; HR = heart rate; NS = not significant; RPP = rate-pressure product; SBP = systolic blood pressure.

TABLE II Hemodynamic Findings at Basal Condition and at Peak Dipyridamole Infusion After Placebo and Propranolol Administration

	Placebo	Propranolol	p Value
Basal			
HR (beats/min)	73 ± 13	58 ± 11	<0.001
SBP (mm Hg)	137 ± 16	135 ± 24	NS
DBP (mm Hg)	86 ± 8	85 ± 12	NS
RPP ($Ux10^{-3}$)	9.95 ± 2.2	7.86 ± 2.3	<0.001
Peak			
HR (beats/min)	94 ± 14	74 ± 13	<0.001
SBP (mm Hg)	147 ± 23	140 ± 28	NS
DBP (mm Hg)	88 ± 11	84 ± 13	NS
RPP ($Ux10^{-3}$)	13.76 ± 3	10.41 ± 3.4	<0.001

Values are mean ± SD.
Abbreviations as in Table I.

TABLE III Hemodynamic Findings After Propranolol Treatment in Patients with Negative (group 1) and Positive (group 2) Echocardiographic Test Results at Peak Dipyridamole Infusion

	Group 1 (13 patients)	Group 2 (8 patients)	p Value
HR (beats/min)	69 ± 12	81 ± 11	<0.02
SBP (mm Hg)	130 ± 24	157 ± 28	<0.05
DBP (mm Hg)	79 ± 12	91 ± 13	<0.005
RPP ($Ux10^{-3}$)	9.02 ± 2.81	12.79 ± 3.22	<0.005

Values are mean ± SD.
Abbreviations as in Table I.

ers of acute myocardial ischemia. Antianginal therapy can reduce the sensitivity of dipyridamole electrocardiographic and dipyridamole echocardiographic testing,[8–10] but not the sensitivity of dipyridamole thallium-201 testing.[11]

In an investigation of the effects of propranolol administration on dipyridamole thallium-201 myocardial perfusion defects in patients with coronary artery disease and scintigraphic criteria of positive dipyridamole test results,[12] β-blockade did not affect dipyridamole thallium-201 images. The disagreement between these data and our results is only apparent. In fact, the diagnostic end point of dipyridamole thallium-201 scintigraphy, linked to the presence of reduced coronary reserve, is referred to different uptake levels of flow tracer. Thus, in some cases dipyridamole-induced myocardial perfusion defects could be the effect of complex redistribution phenomena evoked by the drug and not necessarily the expression of transient myocardial ischemia. On the other hand, wall motion abnormalities, like those induced by dipyridamole infusion are always mechanical markers of transient ischemia because of the presence of significant coronary stenoses associated with a discrepancy between metabolic supply and demand. For this reason, the effects of antianginal therapy on dipyridamole testing could be different if one considers mechanical, electrical or perfusional behavior as an indicator of ischemia.

Mechanisms of dipyridamole-induced ischemia have not been completely clarified. Various studies suggest that dipyridamole-induced coronary vasodilatation could decrease myocardial oxygen supply by complex flow maldistribution phenomena.[13–18]

The rate-pressure product (the main determinant of myocardial oxygen consumption) is only slightly increased during dipyridamole infusion with respect to exercise stress testing. For this reason the role of increased myocardial oxygen demand during dipyridamole stress testing has never been considered one of the mechanisms responsible for transient ischemia.

Many studies have demonstrated that β-adrenoceptor blockers, primarily reducing myocardial oxygen demand during activity or excitement, decrease the frequency of anginal episodes and increase the threshold of effort angina.[19] They may also increase coronary supply through a reduction in extravascular compressive forces.[20]

Benefical effects of β blockers on dipyridamole-induced ischemia are difficult to explain.

Our data show that propranolol significantly reduces heart rate and rate-pressure product at basal condition and at peak dipyridamole infusion with respect to placebo treatment as well as this can be observed during dynamic exercise.[21] We further analyzed these hemodynamic data by subdividing the study population into a group with negative dipyridamole echocardiographic test results and into a group with positive test results after propranolol treatment. Heart rate and rate-pressure product were significantly higher in the group with evidence of dipyridamole-induced asynergies.

This hemodynamic behavior suggests a hypothetic role of myocardial oxygen consumption in dipyridamole-induced ischemia: Dipyridamole could significantly reduce the ischemic threshold by flow maldistribution phenomena in patients with severe coronary artery disease. Under these conditions, slight increases in myocardial oxygen demand could play a role in dipyridamole-induced ischemia. However, propranolol can reverse this ischemia by decreasing oxygen consumption.

β blockers may also abolish dipyridamole-induced ischemia by reverse coronary steal. In patients with obstructive vascular peripheral disease, vascular steal induced by a metabolic vasodilation or by drugs has been seen to be inhibited or even reversed by previous propranolol administration.[22,23] Another experiment demonstrated an improvement in regional myocardial blood flow induced by β blockers in exercise-induced ischemia.[24]

Our data are not sufficient to definitively demonstrate the mechanism of a protective effect of β blocking agents on dipyridamole-induced ischemia. Further investigations are needed to clarify this mechanism by

studying the relation between dipyridamole-induced asynergies, regional coronary flow and myocardial oxygen consumption during propranolol treatment.

Acknowledgment: We wish to thank Giuseppe Biancardi, Liliana Caporaso and Giovanna Santopietro for their technical assistance, and Mary Spears for manuscript revision.

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Analysis of the Signal-Averaged P-Wave Duration in Patients with Percutaneous Coronary Angioplasty–Induced Myocardial Ischemia

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To assess the impact of angioplasty-induced myocardial ischemia on the duration of the surface P wave, patients undergoing elective angioplasty of isolated lesion in the left anterior descending, circumflex or right coronary arteries were monitored with a 3-channel electrocardiographic Holter system. The leads used were modified bipolar chest leads V_5, aVF and V_2 (CM-V_5, CS-aVF and CM-V_2). After electrocardiographic signal-averaging, the earliest onset and the latest offset of the P wave were identified in all of the above time-aligned signal-averaged leads, and the composite maximal P duration was measured under 10 × magnification. The maximal ST-segment shift during balloon inflation was also measured in all of the above leads at 60 ms after the J point. In the study group comprising 47 patients, the mean signal-averaged P-wave duration was 125.0 ± 16 ms at baseline versus 130.0 ± 15 ms during balloon inflation, p <0.005. In the left anterior descending coronary artery group (n = 23), the mean signal-averaged P-wave duration was 122.4 ± 17 ms and 131.3 ± 16 ms during balloon inflation, p <0.005. In the group with a right coronary artery lesion (n = 18), the values were 127.3 ± 14 ms and 128.4 ± 13 ms respectively (p = not significant). Significant increases in the P-wave duration were found to occur in groups both with (n = 34) and without (n = 13) ST-segment shift ≥1 mm (both p <0.05). Thus, the duration of the signal-averaged surface P wave is prolonged during angioplasty-induced ischemia, but significantly so only in the group with left anterior descending coronary artery occlusion.

(Am J Cardiol 1992;70:728–732)

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Measurements of ST-segment deviation have traditionally been used to identify myocardial ischemia on the surface electrocardiogram. The diagnostic yield of this technique has limitations.[1–3] Investigation into new or complementary electrocardiographic variables to better identify ischemia is therefore warranted. The P-wave duration measured in the standard leads and in lead V_1 has been demonstrated to prolong in clinical settings associated with abruptly elevated left ventricular end-diastolic pressure, such as acute myocardial infarction[4] or acute pulmonary edema.[5] The acute elevation in left ventricular end-diastolic pressure, as seen in these conditions, may be reproduced by transient coronary occlusion. This has been demonstrated by Sigwart et al,[6] who showed a marked elevation in the mean left atrial pressure, and end-systolic and end-diastolic atrial volumes with temporary occlusion of the left anterior descending coronary artery during coronary angioplasty. The present study was undertaken to investigate whether angioplasty-induced ischemia would result in a similar increase in the surface P-wave duration.

METHODS

Demographics: The study consisted of 54 consecutive consenting adult patients with 1-vessel coronary artery disease who were undergoing elective coronary angioplasty as a part of their treatment at Long Beach Memorial Medical Center during the period 1987 to 1988. One-vessel disease was defined as 70 to 99% diameter stenosis in the left anterior descending artery or its first diagonal branch, the circumflex artery or its obtuse marginal branch, or the right coronary artery, with no stenosis in another vessel of >50% diameter narrowing. There was no left main stenosis of >30%. All patients had anterograde flow down the significantly stenosed artery at baseline.

Exclusions: Patients were excluded if they (1) became hemodynamically unstable during angioplasty; (2) underwent angioplasty for an acute evolving myocardial infarction; (3) had marked baseline ST-segment and T-wave abnormalities, a ventricular-paced rhythm or bundle branch block; and (3) had atrioventricular junctional rhythm or atrial fibrillation.

Holter techniques: After the skin was shaved and skin surfaces were cleaned with an abrasive solution, radiolucent electrodes were placed on the chest. Electrocardiographic ambulatory monitoring was performed using a Del Mar Avionics 3-channel recorder, model 459 (Del Mar Avionics, Irvine, California). This recorder has a frequency range of 0.05 to 100 Hz at 3 decibels

and has an automatic calibrated signal validation. The gain was adjusted so 0.1 mV = 1 mm. Bipolar lead placements CM-V_2, CM-V_5 and CS-AVF simulating an orthogonal system were used. The 2 positive exploring electrodes were attached in the V_2 and V_5 locations, and the third positive electrode was placed at the left anterior axillary line at the level of the sixth rib (simulating aVF). The negative electrodes were attached to the left and right manubrial border of the sternum for CM-V_2 and CM-V_5, respectively, and the negative electrode of lead CS-AVF was applied in the left infraclavicular fossa. The ground electrode was attached to the upper right chest wall.

P-wave and ST measurements: Baseline recording periods were obtained with the subject in the supine position at least 15 minutes before the commencement of the angioplasty procedure. Patients did not complain of angina at this time. At the onset of balloon inflation, the event marker of the Holter was depressed and the duration of balloon inflation was recorded. These control periods and the periods with increased ST-segment shift (identified in full disclosure printouts of the 3-lead tracings with a speed of 3 mm/s and a gain of 0.1 mV = 0.20 mm) were subsequently averaged on a Del Mar Avionics model 750 analyzer (Del Mar Avionics, Irvine, California) after they were restored to the hard disk from the recording tapes. Signal-averaging was QRS-triggered, and a correlation threshold of 0.98 was used for QRS inclusion in the averaging process. An unfiltered signal was used for analysis. The event marker was used to identify the initiation of balloon inflation, and termination was noted by a repeat depression of the event marker or return of ST-segments to baseline. The printouts of signal-averaged waveforms were obtained at a 100 ms/cm speed and a 0.1 mV/mm calibration.

The maximal ST shift was measured in all 3 leads to the nearest 0.2 mm, 60 ms after the J point, using T-P segment as the isoelectric line. It was measured relative to the patient's own similarly measured baseline ST, from which ST elevation or depression ≥1 mm was considered positive for ischemia. Standard disclosures of the electrocardiogram (25 mm/s and 0.1 mV/mm) were used for measurement under 5× magnification. Analysis of the ST shift was performed independently of the P-wave measurements.

P-wave duration was measured in a blinded fashion by providing the readers with a 2× enlargement of unfiltered, time-aligned, signal-averaged P waves with the ST-T portion of the electrocardiogram eliminated. The 2 blinded readers used a 5× magnifier for measurement (total magnification 10× — this provided the best magnification for identification of P wave onset and offset and its duration measurement). The total atrial activation time was measured on the previously mentioned leads by identifying the earliest onset and the latest offset of the P wave in any lead to the nearest 2 ms (Figure 1). When an individual P wave measured by either observer differed by >10% from the mean value for that P wave, the P wave was rechecked by both observers and a single consensus measurement was recorded.

For purposes of analysis, 1 patient with a diagonal stenosis was included in the left anterior descending group, and 1 patient with an obtuse marginal stenosis was entered into the circumflex group. Patients were classified in groups according to the artery occluded; i.e., left anterior descending, circumflex and right coronary arteries. The presence of any collateral vessels and the left ventricular ejection fraction were obtained at initial angiography, if available. History of a prior myocardial infarction, history of hypertension, and, when possible, the development of anginal pain during balloon inflation were noted. The Holter recording protocol was approved by the Humans Subjects' Review Committee, Long Beach Memorial Medical Center. All subjects gave informed consent.

Statistical analysis: Comparative statistics were calculated using Student's *t* test. The null hypothesis was defined as no difference between groups, and a 2-tailed level of 0.05 was considered statistically significant.

RESULTS

Fifty-four patients undergoing angioplasty were identified as having 1-vessel disease. Patients were excluded because of: (1) hemodynamic instability (n = 2); (2) marked baseline ST-segment and T-wave abnormalities, ventricular-paced rhythm, or bundle branch block (n = 3); and (3) an atrioventricular junctional rhythm (n = 2). The remaining 47 subjects formed the study group. Patient demographics are detailed in Table I and the site of their coronary narrowings listed in Table II. The number of beats averaged at baseline and during angioplasty was 465 ± 125 and 86 ± 77 beats/min, respectively. Heart rate at baseline was 71.1 ± 12 beats/min and the heart rate during inflation was 73.2

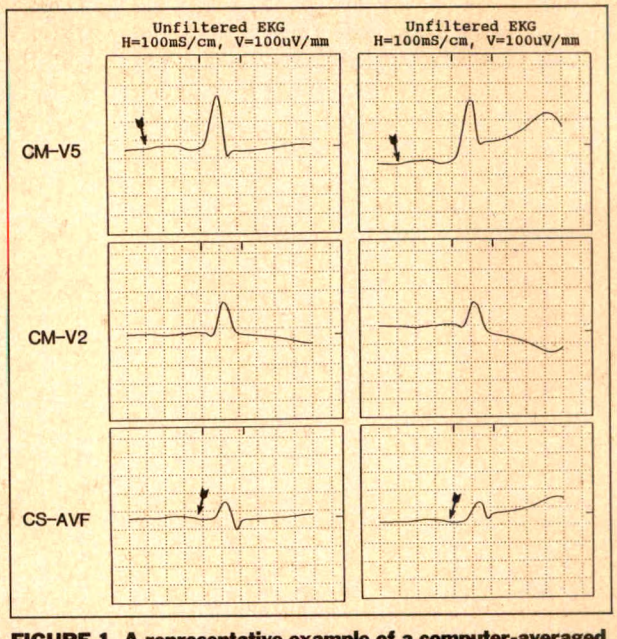


FIGURE 1. A representative example of a computer-averaged and time-aligned P-QRS-ST-T electrocardiographic complex in leads CM-V_5, CM-V_2 and CS-AVF is demonstrated. Baseline complexes are on the *left* of the figure, and complexes during angioplasty are on the *right*. Total atrial activation time was measured by identifying the earliest P-wave onset and the latest offset *(arrows)* in any lead, using 10× magnification. Maximal ST-segment shift was measured at 60 ms after the J point in any 1 of the above leads on the Holter printout (see text). EKG = electrocardiogram.

TABLE I Patient Demographics

Variable	%
Mean age (years)	61 ± 9
Men/women	36/11 (77%/23%)
History of hypertension	16/44 (36%)
History of myocardial infarction	17/42 (40%)
Collateral vessels	8/41 (20%)
Pain during inflation	23/31 (74%)
Left ventricular ejection fraction*	61 ± 12%

*In 23 patients.

TABLE II Site of Coronary Narrowing

Coronary Arteries	Proximal	Mid	Distal	Total
Left anterior descending	10	12	1	23
Left circumflex	2	4	0	6
Right	3	7	8	18

± 14 (p = not significant [NS]). The ability to measure the P-wave duration did not appear to be impacted by balloon inflation; little, if any, extra artifact was noted. In 5 of the cases (11%), P waves were measured by consensus. The 3-lead recording combination revealed an increase in ST-segment shift diagnostic of ischemia (≥1 mm) in any lead in 34 patients (72%).

The mean P-wave duration for all patients at baseline was 125.0 ± 16 ms (1 SD), and was 130.0 ± 15 ms during angioplasty, $p < 0.005$. In the left anterior descending coronary artery group (n = 23), the mean signal-averaged P-wave duration was 122.4 ± 17 ms at baseline and 131.3 ± 16 ms during angioplasty, $p < 0.005$. This is depicted graphically in Figure 2. In the group with circumflex occlusion (n = 6), the values were 127.9 ± 18 ms and 130.5 ± 17 ms, p = NS. In the group with right coronary artery occlusion (n = 18), the values were 127.3 ± 14 ms and 128.4 ± 13 ms, p = NS. There was a significant increase in P-wave duration during inflation in groups both with and without previously visualized collateral vessels, $p < 0.05$. In the group with ≥1 mm ST deviation (n = 34), the P-wave duration increase was significant, from 123.7 ± 15 to 128.7 ± 15 ms, respectively, $p < 0.05$. In the group with ST-segment shift <1 mm (n = 13), a significant P-wave prolongation was similarly noted, with values increasing from 128.4 ± 17 ms to 133.6 ± 16 ms, $p < 0.05$. In the group with prior myocardial infarction, the P-wave duration was also significantly increased with balloon inflation. There were no statistically significant increases in the P-wave duration among the other subgroups, i.e., with right or circumflex artery occlusion, patients without a prior myocardial infarction, or with anginal pain during balloon occlusion (Table III).

DISCUSSION

The reliable detection of ischemia using standard ST criteria remains a difficult clinical problem.[1–3] Little investigation has previously been undertaken to analyze the use of the surface P wave as a "marker of ischemia." This may be because most previous analyses have been performed without the use of signal-averaging. Without the latter, random noise generally obscures the clear identification of P-wave onset and offset. Sophisticated signal-averaging techniques are now available, allowing more accurate measurement of the P-wave duration and other electrocardiographic variables.[7,8]

During sinus rhythm, the latter ⅔ of the surface P wave represents left atrial depolarization. As the left atrium enlarges, the duration of the terminal, posterior and leftward component of the P wave is increased, resulting in P-wave prolongation.[9] Because angioplasty-induced left ventricular ischemia elevates left ventricular end-diastolic pressure[6,10,11] and increases left atrial pressure and size,[5] we hypothesized that left atrial activation time would prolong and would be reflected as an increase in the surface P-wave duration.

It has been demonstrated that left ventricular end-diastolic pressure and left ventricular stiffness are increased during spontaneous episodes of anginal pain,[12] exercise-induced angina pectoris,[13] or pacing-induced

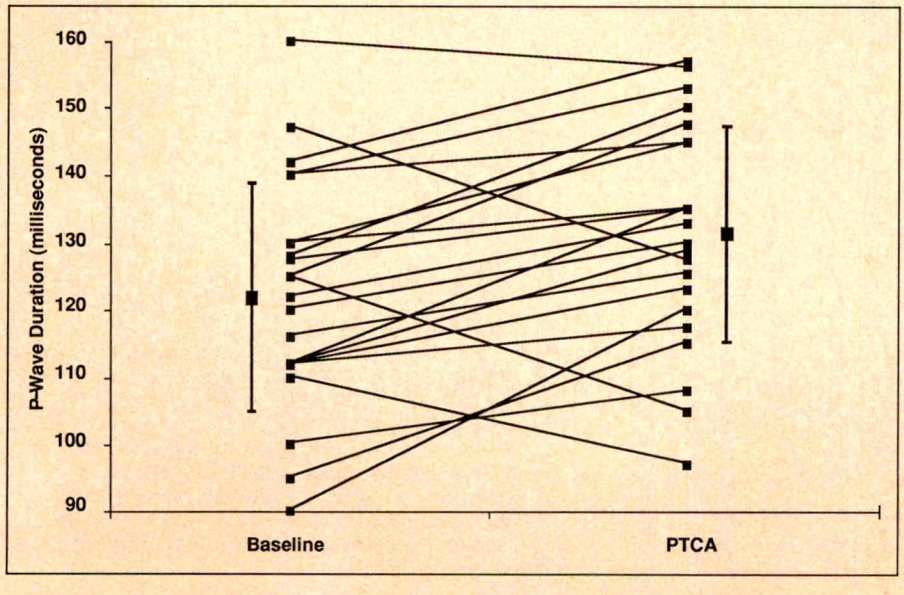


FIGURE 2. Signal-averaged P-wave duration at baseline *(left)* and during balloon occlusion *(right)* in patients with left anterior descending coronary artery occlusion (n = 23). The mean P duration was 122.4 ± 17 ms and 131.3 ± 16 ms, respectively, $p < 0.005$. PTCA = percutaneous transluminal coronary angioplasty.

TABLE III Signal-Averaged P-Wave Duration

Groups	No. of Pts.	P-Wave Duration (ms) Baseline	During PTCA	p Value
All patients	47	125 ± 16	130 ± 15	<0.005
Left anterior descending coronary artery	23	122 ± 17	131 ± 16	<0.005
Left circumflex coronary artery	6	128 ± 18	130 ± 17	NS
Right coronary artery	18	127 ± 14	128 ± 13	NS
Prior myocardial infarction	17	131 ± 15	137 ± 11	<0.05
No history of prior myocardial infarction	25	123 ± 15	127 ± 14	NS
Collateral vessels	8	125 ± 13	134 ± 16	<0.05
No collateral vessels	23	124 ± 16	129 ± 13	<0.05
ST ≥1 mm	34	124 ± 15	129 ± 15	<0.05
ST <1 mm	13	128 ± 17	134 ± 16	<0.05
Pain with inflation	23	129 ± 14	133 ± 15	NS

NS = not significant; PTCA = percutaneous transluminal coronary angioplasty.

angina.[14] Levy et al,[15] performed simultaneous electrocardiographic and pulmonary artery pressure monitoring in patients with coronary disease, and they documented that episodes of ST-segment depression without pain during treadmill exercise, during atrial pacing or unrestricted activity were associated with a significant increase in pulmonary artery diastolic pressure. Chierchia et al[16] also demonstrated that asymptomatic episodes of ST-segment depression or elevation ≥1 mm in patients with unstable angina were accompanied by significant left ventricular end-diastolic and pulmonary artery diastolic pressure elevation.

The increase in P-wave duration demonstrated in the present study most likely relates to an increase in left ventricular end-diastolic pressure with ischemia and a consequent increase in left atrial pressure and volume. Another explanation for the P-wave prolongation is that it is a direct consequence of left atrial wall ischemia, but this is less likely because the mean signal-averaged P-wave duration was not found significantly prolonged in the subgroup with circumflex artery occlusion, and the left atrium is mainly perfused by its branches.[17,18] In our study, the P-wave duration was found significantly increased in the group with left anterior descending coronary artery occlusion, but not in the group with left circumflex or right coronary artery occlusion. This may relate to the larger vascular bed of the left anterior descending artery.[17,18] There are indications in the work by Mizuno et al,[11] that collateral vessels can limit myocardial ischemia during angioplasty. In our study, the P-wave duration was found significantly increased during balloon occlusion, even in the group with previously demonstrated collateral vessels. All patients had 1-vessel coronary artery disease. It would seem intuitive that left ventricular end-diastolic pressure elevation would be accentuated in the presence of multiple-vessel disease because of the higher ischemic burden. The P wave could consequently be further prolonged under these circumstances.

Results in this study are in accordance with our recent findings of the prolongation of the P-wave duration measured on a signal-averaged electrocardiogram during the early recovery phase of a symptom-limited treadmill test in patients with ischemia, and thus help to validate the results of the treadmill study.[8] The present study offers certain advantages: Measurements were obtained on tracings free of any exercise-induced artifacts, and analysis of P-wave duration was not complicated by the T-P and U-P fusion as may occur with increased heart rates.

Study limitations: The 3-lead system used is a "semi-orthogonal" one. It is possible that the X, Y and Z lead system or other lead positions may provide expanded information. Although pain was recorded in patients during balloon inflation, the various uses of minor tranquilizers and opiates restrict the usefulness of this variable for ischemia analysis. In this study, no left ventricular hemodynamic measurements were obtained during angioplasty, so that a relation between left ventricular end-diastolic pressure and P-wave duration could not be tested directly.

Clinical implications: The prolongation of the P-wave duration may prove useful as an additional marker for ischemia detection during ambulatory electrocardiographic monitoring, as well as during exercise or pharmacologic stress testing. The P-wave prolongation in the small group of patients without appreciable ST-segment shift (Table III) is particularly interesting, suggesting that a P-wave duration increase might identify ischemia despite an absence of significant ST-segment shift. Further research is required to answer whether P-wave analysis will provide a clinically useful independent measure of ischemia. A computer algorithm for P-wave onset and offset identification may provide more accurate and consistent measurements and enhance clinical applicability.

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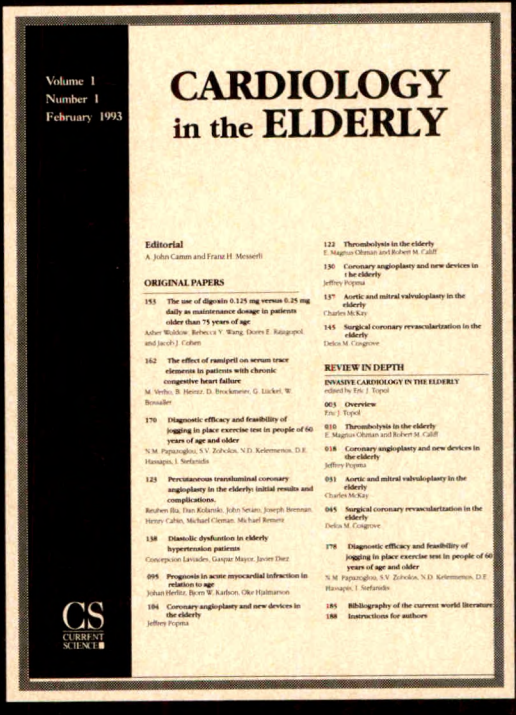
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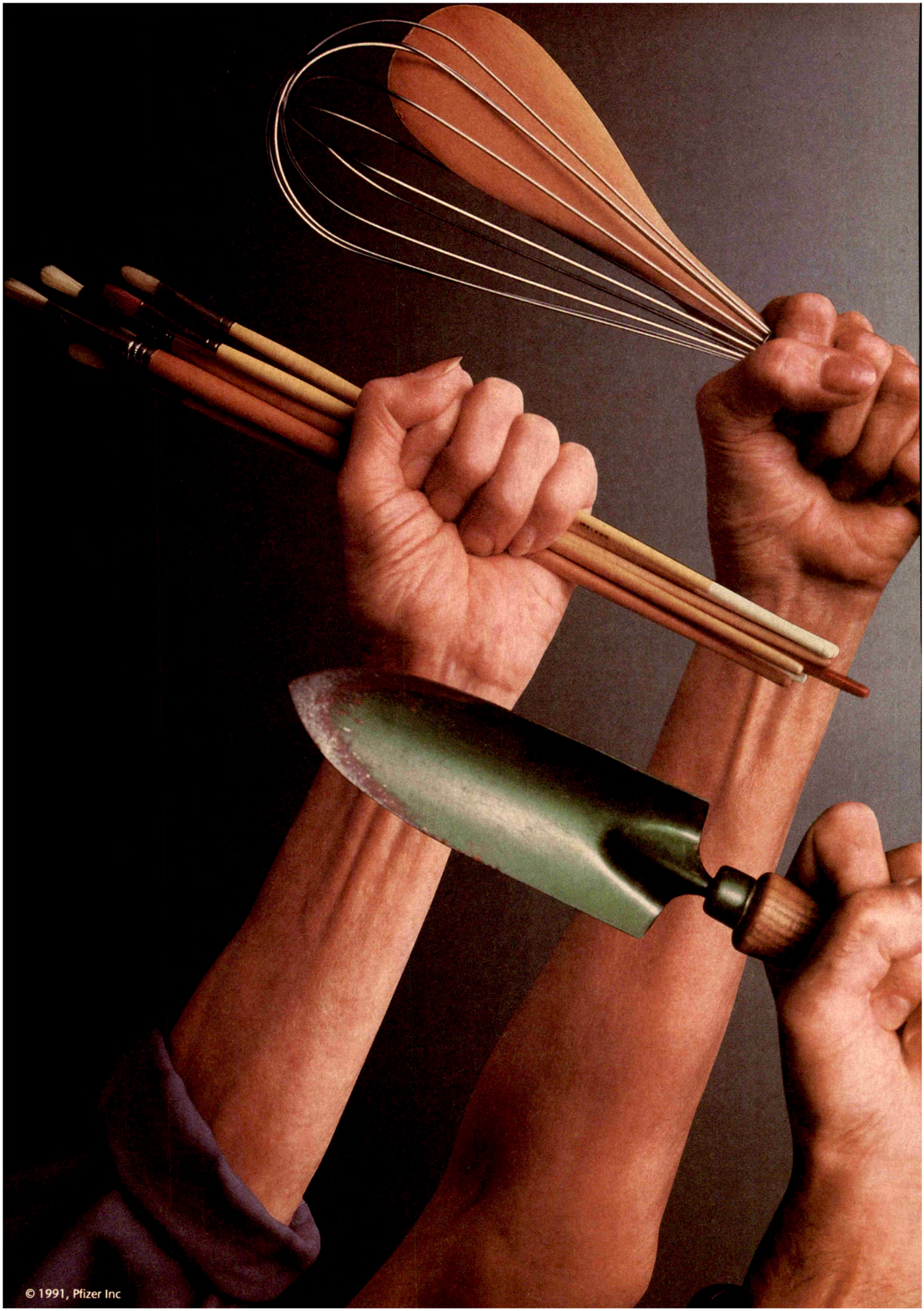
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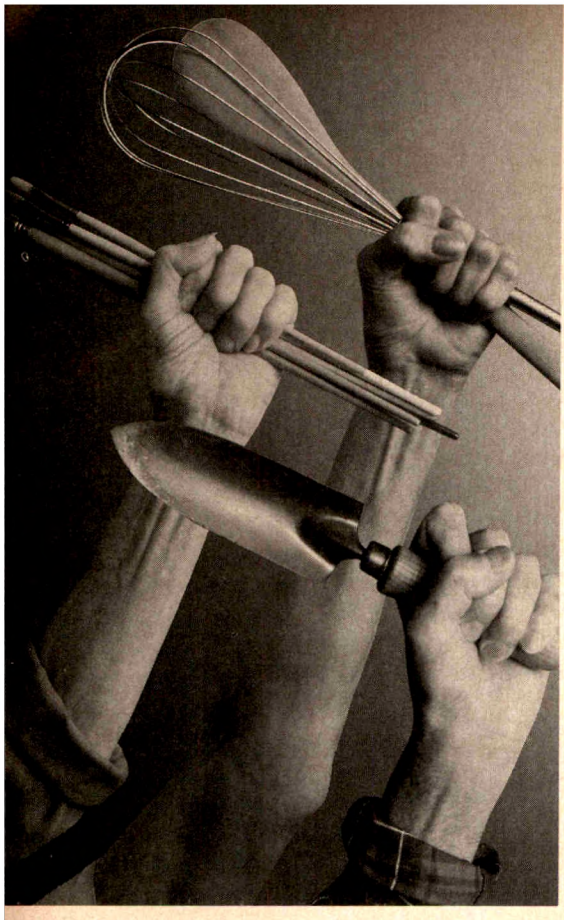
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Brief Summary

PROCARDIA XL® (nifedipine) Extended Release Tablets For Oral Use

CONTRAINDICATIONS: Known hypersensitivity reaction to nifedipine.

WARNINGS: Excessive Hypotension: Although in most angina patients the hypotensive effect of nifedipine is modest and well tolerated, occasional patients have had excessive and poorly tolerated hypotension. These responses have usually occurred during initial titration or at the time of subsequent upward dosage adjustment, and may be more likely in patients on concomitant beta blockers.

Severe hypotension and/or increased fluid volume requirements have been reported in patients receiving nifedipine together with a beta-blocking agent who underwent coronary artery bypass surgery using high dose fentanyl anesthesia. The interaction with high dose fentanyl appears to be due to the combination of nifedipine and a beta blocker, but the possibility that it may occur with nifedipine alone, with low doses of fentanyl, in other surgical procedures, or with other narcotic analgesics cannot be ruled out. In nifedipine-treated patients where surgery using high dose fentanyl anesthesia is contemplated, the physician should be aware of these potential problems and if the patient's condition permits, sufficient time (at least 36 hours) should be allowed for nifedipine to be washed out of the body prior to surgery.

The following information should be taken into account in those patients who are being treated for hypertension as well as angina:

Increased Angina and/or Myocardial Infarction: Rarely, patients, particularly those who have severe obstructive coronary artery disease, have developed well documented increased frequency, duration and/or severity of angina or acute myocardial infarction on starting nifedipine or at the time of dosage increase. The mechanism of this effect is not established.

Beta Blocker Withdrawal: It is important to taper beta blockers if possible, rather than stopping them abruptly before beginning nifedipine. Patients recently withdrawn from beta blockers may develop a withdrawal syndrome with increased angina, probably related to increased sensitivity to catecholamines. Initiation of nifedipine treatment will not prevent this occurrence and on occasion has been reported to increase it.

Congestive Heart Failure: Rarely, patients usually receiving a beta blocker, have developed heart failure after beginning nifedipine. Patients with tight aortic stenosis may be at greater risk for such an event, as the unloading effect of nifedipine would be expected to be of less benefit to those patients, owing to their fixed impedance to flow across the aortic valve.

PRECAUTIONS: General—Hypotension: Because nifedipine decreases peripheral vascular resistance, careful monitoring of blood pressure during the initial administration and titration of nifedipine is suggested. Close observation is especially recommended for patients already taking medications that are known to lower blood pressure. (See WARNINGS.)

Peripheral Edema: Mild to moderate peripheral edema occurs in a dose dependent manner with an incidence ranging from approximately 10% to about 30% at the highest dose studied (180 mg). It is a localized phenomenon thought to be associated with vasodilation of dependent arterioles and small blood vessels and not due to left ventricular dysfunction or generalized fluid retention. With patients whose angina or hypertension is complicated by congestive heart failure, care should be taken to differentiate this peripheral edema from the effects of increasing left ventricular dysfunction.

Other: As with any other non-deformable material, caution should be used when administering PROCARDIA XL in patients with preexisting severe gastrointestinal narrowing (pathologic or iatrogenic). There have been rare reports of obstructive symptoms in patients with known strictures in association with the ingestion of PROCARDIA XL.

Laboratory Tests: Rare, usually transient, but occasionally significant elevations of enzymes such as alkaline phosphatase, CPK, LDH, SGOT, and SGPT have been noted. The relationship to nifedipine therapy is uncertain in most cases, but probable in some. These laboratory abnormalities have rarely been associated with clinical symptoms; however, cholestasis with or without jaundice has been reported. A small (5.4%) increase in mean alkaline phosphatase was noted in patients treated with PROCARDIA XL. This was an isolated finding not associated with clinical symptoms and it rarely resulted in values which fell outside the normal range. Rare instances of allergic hepatitis have been reported. In controlled studies, PROCARDIA XL did not adversely affect serum uric acid, glucose, or cholesterol. Serum potassium was unchanged in patients receiving PROCARDIA XL in the absence of concomitant diuretic therapy, and slightly decreased in patients receiving concomitant diuretics.

Nifedipine, like other calcium channel blockers, decreases platelet aggregation *in vitro.* Limited clinical studies have demonstrated a moderate but statistically significant decrease in platelet aggregation and increase in bleeding time in some nifedipine patients. This is thought to be a function of inhibition of calcium transport across the platelet membrane. No clinical significance for these findings has been demonstrated.

Positive direct Coombs test with/without hemolytic anemia has been reported but a causal relationship between nifedipine administration and positivity of this laboratory test, including hemolysis, could not be determined.

Although nifedipine has been used safely in patients with renal dysfunction and has been reported to exert a beneficial effect in certain cases, rare reversible elevations in BUN and serum creatinine have been reported in patients with pre-existing chronic renal insufficiency. The relationship to nifedipine therapy is uncertain in most cases but probable in some.

Drug Interactions—Beta-adrenergic blocking agents: (See WARNINGS) Experience in over 1400 patients with Procardia® capsules in a noncomparative clinical trial has shown that concomitant administration of nifedipine and beta-blocking agents is usually well tolerated but there have been occasional literature reports suggesting that the combination may increase the likelihood of congestive heart failure, severe hypotension, or exacerbation of angina.

Long Acting Nitrates: Nifedipine may be safely co-administered with nitrates, but there have been no controlled studies to evaluate the antianginal effectiveness of this combination.

Digitalis: Administration of nifedipine with digoxin increased digoxin levels in nine of twelve normal volunteers. The average increase was 45%. Another investigator found no increase in digoxin levels in thirteen patients with coronary artery disease. In an uncontrolled study of over two hundred patients with congestive heart failure during which digoxin blood levels were not measured, digitalis toxicity was not observed. Since there have been isolated reports of patients with elevated digoxin levels, it is recommended that digoxin levels be monitored when initiating, adjusting, and discontinuing nifedipine to avoid possible over- or under-digitalization.

Coumarin Anticoagulants: There have been rare reports of increased prothrombin time in patients taking coumarin anticoagulants to whom nifedipine was administered. However, the relationship to nifedipine therapy is uncertain.

Cimetidine: A study in six healthy volunteers has shown a significant increase in peak nifedipine plasma levels (80%) and area under-the-curve (74%), after a one week course of cimetidine at 1000 mg per day and nifedipine at 40 mg per day. Ranitidine produced smaller, non-significant increases. The effect may be mediated by the known inhibition of cimetidine on hepatic cytochrome P-450, the enzyme system probably responsible for the first-pass metabolism of nifedipine. If nifedipine therapy is initiated in a patient currently receiving cimetidine, cautious titration is advised.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Nifedipine was administered orally to rats, for two years and was shown to be carcinogenic. When given to rats prior to mating, nifedipine caused reduced fertility at a dose approximately 30 times the maximum recommended human dose. *In vivo* mutagenicity studies were negative.

Pregnancy: Pregnancy Category C. Nifedipine has been shown to be teratogenic in rats when given in doses 30 times the maximum recommended human dose. Nifedipine was embryotoxic (increased fetal resorptions, decreased fetal weight, increased stunted forms, increased fetal deaths, decreased neonatal survival) in rats, mice, and rabbits at doses of from 3 to 10 times the maximum recommended human dose. In pregnant monkeys, doses 2/3 and twice the maximum recommended human dose resulted in small placentas and underdeveloped chorionic villi. In rats, doses three times maximum human dose and higher caused prolongation of pregnancy. There are no adequate and well controlled studies in pregnant women. PROCARDIA XL® (nifedipine) Extended Release Tablets should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

ADVERSE EXPERIENCES: Over 1000 patients from both controlled and open trials with PROCARDIA XL Extended Release Tablets in hypertension and angina were included in the evaluation of adverse experiences. All side effects reported during PROCARDIA XL Extended Release Tablet therapy were tabulated independent of their causal relation to medication. The most common side effects reported with PROCARDIA XL was edema which was dose related and ranged in frequency from approximately 10% to about 30% at the highest dose studied (180 mg). Other common adverse experiences reported in placebo-controlled trials include: headache (15.8%, compared to 9.8% placebo incidence), fatigue (5.9%, compared to 4.1% placebo incidence), dizziness (4.1%, compared to 4.5% placebo incidence), constipation (3.3%, compared to 2.3% placebo incidence), and nausea (3.3%, compared to 1.7% placebo incidence). Of these, only edema and headache were more common in PROCARDIA XL patients than placebo patients.

The following adverse reactions occurred with an incidence of less than 3.0%. With the exception of leg cramps, the incidence of these side effects was similar to that of placebo alone: *body as a whole/systemic*: asthenia, flushing, pain; *cardiovascular*: palpitations; *central nervous system*: insomnia, nervousness, paresthesia, somnolence; *dermatologic*: pruritus, rash; *gastrointestinal*: abdominal pain, diarrhea, dry mouth, dyspepsia, flatulence; *musculoskeletal*: arthralgia, leg cramps; *respiratory*: chest pain (nonspecific), dyspnea; *urogenital*: impotence, polyuria.

Other adverse reactions were reported sporadically with an incidence of 1.0% or less. These include: *body as a whole/systemic*: face edema, fever, hot flashes, malaise, periorbital edema, rigors; *cardiovascular*: arrhythmia, hypotension, increased angina, tachycardia, syncope; *central nervous system*: anxiety, ataxia, decreased libido, depression, hypertonia, hypoesthesia, migraine, paroniria, tremor, vertigo; *dermatologic*: alopecia, increased sweating, urticaria, purpura; *gastrointestinal*: eructation, gastric esophageal reflux, gum hyperplasia, melena, vomiting, weight increase; *musculoskeletal*: back pain, gout, myalgias; *respiratory*: coughing, epistaxis, upper respiratory tract infection, respiratory disorder, sinusitis; *special senses*: abnormal lacrimation, abnormal vision, taste perversion, tinnitus; *urogenital/reproductive*: breast pain, dysuria, hematuria, nocturia.

Adverse experiences which occurred in less than 1 in 1000 patients cannot be distinguished from concurrent disease states or medications.

The following adverse experiences, reported in less than 1% of patients, occurred under conditions (e.g., open trials, marketing experience) where a causal relationship is uncertain: gastrointestinal irritation, gastrointestinal bleeding.

In multiple-dose U.S. and foreign controlled studies with nifedipine capsules in which adverse reactions were reported spontaneously, adverse effects were frequent but generally not serious and rarely required discontinuation of therapy or dosage adjustment. Most were expected consequences of the vasodilator effects of Procardia. Adverse experiences reported in placebo-controlled trials include: dizziness, lightheadedness, and giddiness (27%, compared to 15% placebo incidence); flushing, heat sensation (25%, compared to 8% placebo incidence); headache (23%, compared to 20% placebo incidence); weakness (12%, compared to 10% placebo incidence); nausea, heartburn (11%, compared to 8% placebo incidence); muscle cramps, tremor (8% compared to 3% placebo incidence); peripheral edema (7%, compared to 1% placebo incidence); nervousness, mood change (7%, compared to 4% placebo incidence); palpitation (7%, compared to 5% placebo incidence); dyspnea, cough, and wheezing (6%, compared to 3% placebo incidence); and nasal congestion, sore throat (6%, compared to 3% placebo incidence).

There is also a large uncontrolled experience in over 2100 patients in the United States. Most of the patients had vasospastic resistant angina pectoris, and about half had concomitant treatment with beta-adrenergic blocking agents. The relatively common adverse events were similar in nature to those seen with PROCARDIA XL.

In addition, more serious adverse events were observed, not readily distinguishable from the natural history of the disease in these patients. It remains possible, however, that some or many of these events were drug related. Myocardial infarction occurred in about 4% of patients and congestive heart failure or pulmonary edema in about 2%. Ventricular arrhythmias or conduction disturbances each occurred in fewer than 0.5% of patients.

In a subgroup of over 1000 patients receiving Procardia with concomitant beta blocker therapy, the pattern and incidence of adverse experiences was not different from that of the entire group of Procardia treated patients (See PRECAUTIONS.)

In a subgroup of approximately 250 patients with a diagnosis of congestive heart failure as well as angina, dizziness or lightheadedness, peripheral edema, headache or flushing each occurred in one in eight patients. Hypotension occurred in about one in 20 patients. Syncope occurred in approximately one patient in 250. Myocardial infarction or symptoms of congestive heart failure each occurred in about one patient in 15. Atrial or ventricular dysrhythmias each occurred in about one patient in 150.

In post-marketing experience, there have been rare reports of exfoliative dermatitis caused by nifedipine.

More detailed professional information available on request. Revised July 19

Pfizer Labs

Relation of High-Density Lipoprotein Cholesterol and Triglycerides to Incidence of Atherosclerotic Coronary Artery Disease (the PROCAM Experience)

Gerd Assmann, MD, and Helmut Schulte, Dr rer medic

The incidence of atherosclerotic coronary artery disease (CAD) was assessed in 4,559 male participants (aged 40 to 64 years) from the Prospective Cardiovascular Münster study, over a 6-year follow-up period. During this time, 186 study participants developed atherosclerotic CAD (134 definite nonfatal myocardial infarctions and 52 definite atherosclerotic CAD deaths including 21 sudden cardiac deaths and 31 fatal myocardial infarctions). Univariate analysis revealed a significant association between the incidence of atherosclerotic CAD and high-density lipoprotein (HDL) cholesterol ($p < 0.001$) and triglycerides ($p < 0.001$). The relation to HDL cholesterol remained after adjustment for other risk factors. By contrast, the relation between the incidence of atherosclerotic CAD and triglycerides disappeared if, in a multivariate analysis by means of a multiple logistic function, cholesterol or HDL cholesterol were taken into account. However, the data suggested that hypertriglyceridemia is a powerful additional coronary risk factor, when excessive triglycerides coincide with a high ratio of plasma low-density lipoprotein cholesterol to HDL cholesterol (>5.0). Even though the prevalence of this subgroup was only 4.3%, it included a quarter of all atherosclerotic CAD events observed.

(Am J Cardiol 1992;70:733–737)

Although the causal connection between hypercholesterolemia and atherosclerosis is well understood, the potential relation between elevated triglyceride levels or decreased high-density lipoprotein (HDL) cholesterol levels and atherosclerotic coronary artery disease (CAD) remains controversial. Triglycerides are not listed as a cardiovascular risk factor in the National Cholesterol Education Program guidelines[1]; by contrast, the European classification of hyperlipidemia is based on the simultaneous determination of both cholesterol and triglycerides and it is argued in these guidelines that mixed hyperlipidemia (group D, cholesterol 200 to 300 mg/dl and triglycerides 200 to 500 mg/dl) deserves particular attention.[2] In a recently published position paper, an international committee summarized the findings on hypertriglyceridemia as a risk factor for cardiovascular disease with the intention of stimulating discussion on the role of triglycerides in this disorder.[3] To further investigate the relation between triglycerides and/or HDL cholesterol and the risk of atherosclerotic CAD, data obtained from 186 patients with definite nonfatal myocardial infarction or definite atherosclerotic CAD death in the course of a 6-year-follow-up period (the Prospective Cardiovascular Münster [PROCAM] study) were compared with data from 4,221 subjects not affected by atherosclerotic CAD and are presented here.

METHODS

Description of the Prospective Cardiovascular Münster study: In the PROCAM study, people at work (employees of 52 companies and authorities) were examined for cardiovascular risk factors and then kept under observation to record mortality as well as cardiovascular events including myocardial infarction and stroke. The examination at study entry included case history using standardized questionnaires, measurement of blood pressure and anthropometric data, a resting electrocardiogram and collection of a blood sample after a 12-hour fast for the determination of >20 laboratory parameters. The examination was performed during paid working hours. Participation was voluntary (between 40 and 80% took part, average 60%), and free of charge to both volunteers and their employers (apart from loss of work). All findings were reported to the participant's general practitioner, and the volunteer was told whether the results of the examination were normal, or whether a check-up by the general practitioner might be necessary. The investigators neither carried out nor arranged for any intervention.

From the Institut für Arteriosklerosеforschung an der Universität Münster, Münster; and the Institut für Klinische Chemie und Laboratoriumsmedizin, Zentrallaboratorium der Universität Münster, Münster, Germany. This study was supported by Bundesministerium für Forschung und Technologie, Bonn, Ministerium für Wissenschaft und Forschung NRW, Düsseldorf, Deutsche Forschungsgemeinschaft, Bonn, and Landesversicherungsanstalt (LVA) Westfalen, Münster. Manuscript received February 20, 1992; revised manuscript received May 27, 1992, and accepted May 28.

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The recommendations of American and British Heart Associations were followed for measuring blood pressure.[4] Systolic and diastolic readings were measured on the left arm with the subject seated and the arm at heart level. One measurement was taken at the start of the interview by the examining physician and one was taken at the end of the interview. The second measurement was recorded.

Total cholesterol, triglycerides and HDL cholesterol were measured using enzymatic assays and (for HDL cholesterol) a precipitation method from Boehringer Mannheim, Federal Republic of Germany, on a Hitachi 737 autoanalyzer.[5] Low-density lipoprotein (LDL) cholesterol was calculated by the Friedewald formula if triglycerides were <400 mg/dl.[6] A subject was said to have glucose intolerance if a diagnosis of diabetes mellitus was known or if glucose in the specimen of whole fasting blood was ≥120 mg/dl. History of cigarette smoking was obtained in the interview. Anyone smoking cigarettes within the last 12 months was considered a current smoker. Electrocardiograms were recorded with the subject in the recumbent position. Twelve leads were used: 3 standard, 3 augmented unipolar link leads, and 6 precordial leads of Wilson. Further methods used for the examinations[7] and the laboratory tests[5] are described in detail elsewhere.

Follow-up: Questionnaires were sent to participants every 2 years to determine the occurrence of myocardial infarction, stroke or death. At the initial examination, participants were told that they would obtain a questionnaire every 2 years. The response rate to these questionnaires was 96% after 2 reminders each by mail and phone if necessary. The death certificate was reviewed if a study participant died. For all mortality and morbidity data obtained from the questionnaire, we requested hospital records and records from the attending physician, as well as an eyewitness account of deaths, so that a critical event committee could verify the diagnosis or cause of death. The initial examination was repeated after 6 to 7 years.

For the following analyses 2 end points were considered: definite nonfatal myocardial infarction and definite atherosclerotic CAD death including sudden cardiac death and fatal myocardial infarction.

Sudden cardiac death was diagnosed if a subject, apparently well, was observed to have died within 1 hour of onset of symptoms or within 1 hour of having last been seen without them, and the cause of death could not reasonably be attributed (on the basis of the full clinical information) to violence, trauma or some potentially lethal disease other than CAD. Fatal myocardial infarction was diagnosed when a death certificate or hospital record described the cause of death and there was either preterminal hospitalization with definite or suspect myocardial infarction (see next) or an autopsy finding of acute myocardial infarction.

Definite nonfatal myocardial infarction was designated if ≥1 of the following categories were fulfilled:

1. Diagnostic electrocardiogram at the time of the event.
2. Ischemic cardiac pain (severe substernal pain having a deep or visceral quality and lasting for >30 minutes) and diagnostic enzymes.
3. Ischemic cardiac pain and equivocal enzymes and equivocal electrocardiogram.
4. An electrocardiogram is diagnostic for myocardial infarction, although a previous one was not.

An electrocardiogram at the time of the event was considered diagnostic if either of the following were present: (1) unequivocal Q or QS pattern, Minnesota code 1-1; and (2) Q or QS pattern (codes 1-2-1 to 1-2-7) plus any T-wave item (codes 5-1 to 5-3). Only criterion 1 applies in the presence of ventricular conduction defects.

An electrocardiogram at the time of the event was considered equivocal if any of the following was present: (1) Q or QS pattern (codes 1-2-1 to 1-2-7); (2) ST-junction and ST-segment depression (codes 4-1 to 4-3); (3) T-wave item (codes 5-1 to 5-2); and (4) left bundle branch block (code 7-1).

Enzymes determined coexistent with the event were considered diagnostic if creatine kinase, serum glutamic oxaloacetic transaminase, or lactic dehydrogenase values, or a combination of these, were ≥2 times the upper limit of the local laboratory but ≤15 times that value. Enzymes determined coexistent with the event were considered equivocal if ≥1 of the determined enzymes was elevated but did not fulfill criteria for diagnostic enzymes.

Suspected CAD death was diagnosed (1) if a death certificate described CAD and there was neither adequate preterminal documentation of the event nor a previous diagnosis of atherosclerotic CAD; or (2) if the terminal episode lasted between 1 and 24 hours, and available information implied that the cause of death was probably CAD and no other cause could be ascribed.

Patients were classified as having "suspect myocardial infarction" if ≥1 of the following categories were fulfilled: (1) ischemic cardiac pain; (2) diagnostic enzymes; (3) equivocal electrocardiogram and equivocal enzymes; and (4) equivocal electrocardiogram alone, provided that it was not based on ST- or T-wave changes only.

The study began in 1979 and the recruitment phase was completed at the end of 1985. Full data records are held on a total of 19,698 participants in the PROCAM study (age range 16 to 65 years). In the study, 13,737 men had an average age of 41.4 ± 11.2 years and the 5,961 women were aged 36.6 ± 12.5 years ($p < 0.001$).

Statistics: An explorative analysis was performed using the statistical package for the social sciences (SPSS-X)[8] and the statistical analysis system (SAS).[9] Comparisons between groups were performed with the Mann-Whitney U test for continuous variables and with the chi-square test for discrete variables. The relation between a variable and risk of atherosclerotic CAD was described by dividing the patient series into tertiles of the studied variable and then calculating the incidence rate for each tertile. As is usual in prospective studies of CAD the simultaneous contributions of several factors

to the risk of major ischemic heart disease were analyzed using a multiple logistic model.

RESULTS

Incidence of coronary artery disease: An adequate incidence of atherosclerotic CAD in the PROCAM study occurred only in men aged ≥40 years. The analysis described next was confined to 4,559 male participants aged between 40 and 65 years, without a prior history of myocardial infarction or stroke, and with a follow-up period of 6 years. In this group, 134 definite nonfatal myocardial infarctions and 52 definite atherosclerotic CAD deaths were recorded including 21 sudden cardiac deaths and 31 fatal myocardial infarctions (group CAD+). Ten suspect CAD deaths occurred and 119 men died from causes other than CAD (11 from other diseases of the circulatory system, 54 from malignant neoplasms, 24 from other diseases and 30 from accidents and violence). The number of nonfatal strokes was 23, whereas 4,221 subjects survived the 6 years after initial examination without definite nonfatal myocardial infarction or stroke (group CAD−), including 38 with suspect nonfatal myocardial infarction. The age-standardized mean values for risk factors within groups CAD+ and CAD− are listed in Table I. The numbers of observed definite events per tertile of relevant variables are given in Table II.

High-density lipoprotein cholesterol: The 4,221 subjects not affected by atherosclerotic CAD (group CAD−) had an age-standardized mean HDL cholesterol level of 45.2 ± 11.8 mg/dl, whereas subjects with definite nonfatal myocardial infarctions or death attributed to atherosclerotic CAD (group CAD+) had a significantly ($p < 0.001$) lower mean HDL cholesterol level (39.5 ± 10.6 mg/dl). In the CAD+ group, 45% of participants had HDL cholesterol levels <35 mg/dl; in the CAD− group 16% of subjects had levels below this limit. The numbers of observed definite events per tertile of the HDL cholesterol distribution were 77, 27 and 26/1,000 subjects within 6 years, respectively.

Triglycerides: The geometric mean of triglyceride level in nonaffected subjects was 134.5 mg/dl (median 129.9), whereas the geometric mean of triglyceride level in the CAD+ group was significantly ($p < 0.001$) higher, 163.0 mg/dl (median 161.5). In the CAD− group, 22% of participants had triglyceride levels ≥200 mg/dl; in the CAD+ group 40% of subjects exceeded this limit. The numbers of observed definite events per tertile of the triglyceride distribution were 28, 39 and 60/1,000 subjects within 6 years, respectively.

Multivariate analysis: In logistic function analyses, HDL cholesterol ($p < 0.001$) and log-transformed values of triglycerides ($p < 0.01$) were significantly associated with the incidence of atherosclerotic CAD. Although the correlation with HDL cholesterol remained after adjustment for other risk factors, triglyceride levels no longer correlated significantly with atherosclerotic CAD, if in a multivariate analysis by means of a multiple logistic function, cholesterol or HDL cholesterol levels were taken into account. However, hypertriglyceridemia (≥200 mg/dl) was associated with markedly higher incidence rates of definite events in subgroups with higher cholesterol (Figure 1), LDL cholesterol (Figure 2) levels, or lower HDL cholesterol levels (Figure 3). In subjects with LDL cholesterol levels ≥160 mg/dl, concomitant hypertriglyceridemia increased the

TABLE I Mean Values of Age-Standardized Factors for Male Participants (aged 40 to 65 years) in the PROCAM Study, With (CAD+) and Without (CAD−) Development of Atherosclerotic CAD Within Six Years

Variable	CAD− (n = 4,221)	CAD+ (n = 186)	p Value
Cholesterol (mg/dl)	222.9 (41.0)	251.8 (47.3)	<0.001
HDL cholesterol (mg/dl)	45.2 (11.8)	39.5 (10.6)	<0.001
LDL cholesterol (mg/dl)*	147.1 (35.9)	176.2 (39.5)	<0.001
Triglycerides (mg/dl)†	134.5	163.0	<0.001
Systolic blood pressure (mm Hg)	132.7 (18.9)	139.4 (21.2)	<0.001
Diastolic blood pressure (mm Hg)	86.3 (11.1)	89.5 (12.7)	<0.01
Body mass index (kg/m^2)	26.3 (3.0)	26.7 (2.9)	<0.05
No. of cigarette smokers	1317 (31.2%)	98 (52.7%)	<0.001

*n = 4,086 in CAD− subjects, and n = 177 in CAD+ subjects.
†Geometric mean.
Values are mean ± standard deviation (in brackets) unless otherwise indicated.
CAD = coronary artery disease; HDL = high-density lipoprotein; LDL = low-density lipoprotein; PROCAM = Prospective Cardiovascular Münster study.

TABLE II Incidence of Atherosclerotic Coronary Artery Disease (n = 186) Within Six Years of Initial Examination in Tertiles of Age-Standardized Factors for Male Participants aged 40 to 65 Years (n = 4,407) in the PROCAM Study

Variable	Tertile Cut-Off Points	CAD Incidence (%) in: Lower Tertile	Middle Tertile	Upper Tertile	p Value
Cholesterol (mg/dl)	<205 and >239	2.1	3.4	7.2	<0.001
HDL cholesterol (mg/dl)	<39 and >48	7.7	2.7	2.6	<0.001
LDL cholesterol (mg/dl)*	<132 and >162	1.7	2.8	8.0	<0.001
Triglycerides (mg/dl)	<105 and >166	2.8	3.9	6.0	<0.001
Systolic blood pressure (mm Hg)	<124 and >138	3.1	3.6	5.7	<0.001
Body mass index (kg/m^2)	<25.0 and >27.2	3.3	4.2	5.3	<0.05

*n = 4,263; 177 incidences of atherosclerotic coronary artery disease.
Abbreviations as in Table I.

incidence rate of definite CAD by approximately 2.5-fold. Further, the subgroup of PROCAM participants with an elevated LDL cholesterol/HDL cholesterol ratio (>5.0, prevalence 11.4%) had a markedly increased risk of definite events (165/1,000 subjects in 6 years) compared with men with a lower ratio (≤5.0, incidence 26/1,000 subjects in 6 years). In both subgroups incidence rates were higher in hypertriglyceridemic subjects (Figure 4). In particular, the hypertriglyceridemic subgroup with an elevated LDL cholesterol/HDL cholesterol ratio had the highest risk of atherosclerotic CAD. Even though only 4.3% of participants were in this subgroup, it accounted for a quarter of all definite events observed. The proportion of men with diabetes mellitus (known diabetes mellitus or elevated fasting blood glucose (≥120 mg/dl)), hypertension (systolic blood pressure ≥160 mm Hg, or diastolic blood pressure ≥95 mm Hg), or any combination of these, in this high-risk group was 16 and 43%, respectively. These proportions were significantly higher than in the remaining group with 8 and 31%, respectively.

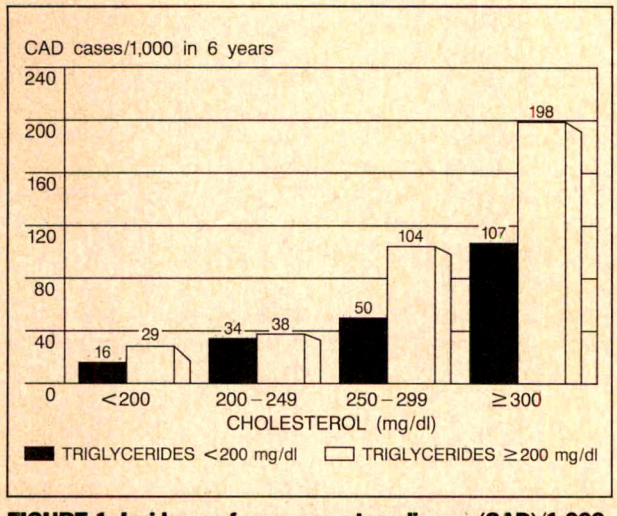


FIGURE 1. Incidence of coronary artery disease (CAD)/1,000 subjects over a 6-year period according to triglycerides and cholesterol levels.

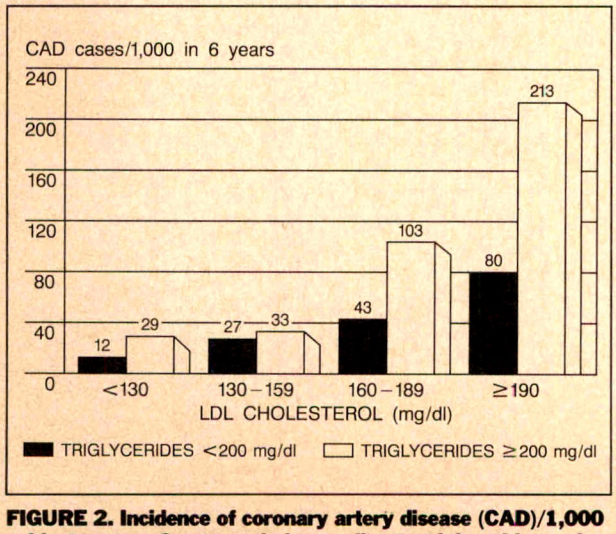


FIGURE 2. Incidence of coronary artery disease (CAD)/1,000 subjects over a 6-year period according to triglycerides and low-density lipoprotein (LDL) cholesterol levels.

DISCUSSION

Existing evidence concerning hypertriglyceridemia and CAD is summarized by the "international committee for the evaluation of hypertriglyceridemia as a vascular risk factor."[3] Most prospective studies have shown a positive correlation between elevated serum triglyceride levels and CAD risk, particularly in women and in patients with non-insulin-dependent diabetes. Only a few studies did not find this univariate association between triglyceride levels and the incidence of CAD in men. Also, patients with angiographically documented CAD and survivors of myocardial infarction have consistently been found to have elevated serum triglyceride levels, although it must be taken into account that lipid levels change after acute myocardial infarction.[10] The results of multivariate analysis are more divergent, with the triglyceride association persisting after the adjustment for total cholesterol or LDL cholesterol in most studies but disappearing in a few studies. In studies controlling for the significant effects of HDL cholesterol

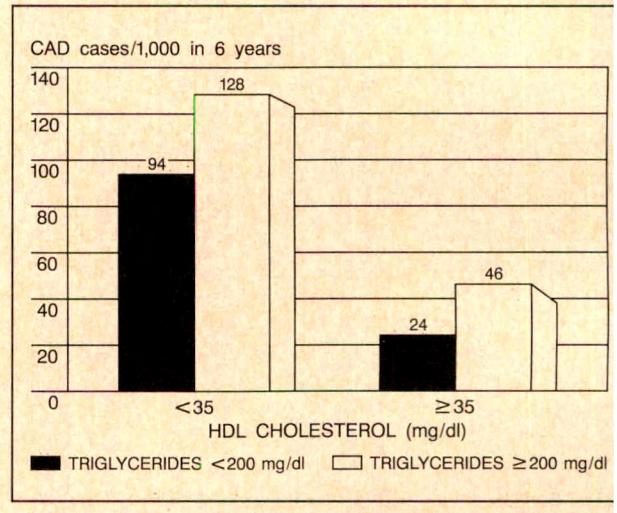


FIGURE 3. Incidence of coronary artery disease (CAD)/1,000 subjects over a 6-year period according to triglycerides and high-density lipoprotein (HDL) cholesterol levels.

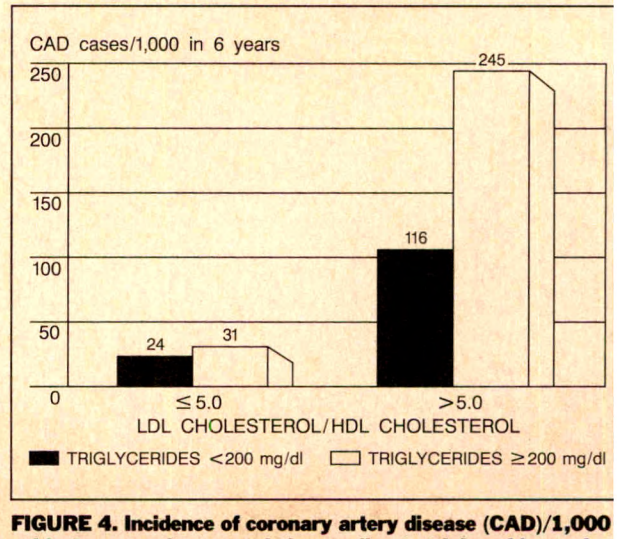


FIGURE 4. Incidence of coronary artery disease (CAD)/1,000 subjects over a 6-year period according to triglycerides and low-density lipoprotein (LDL) cholesterol/high-density lipoprotein (HDL) cholesterol ratio.

the link between elevated serum triglycerides and CAD breaks down.

The level of HDL cholesterol in plasma has been shown to be inversely related to the incidence of CAD in several prospective epidemiologic studies.[11–19] In accordance with our findings, in 6 of these studies[11–16] this inverse association was statistically significant and remained so after adjustment for other risk factors.

According to the results of the PROCAM study, the prediction of risk for myocardial infarction or CAD death cannot be based on LDL cholesterol determinations alone. At moderately (160 to 189 mg/dl) and severely (≥190 mg/dl) elevated LDL cholesterol concentrations, the risk of atherosclerotic CAD increased approximately 2.5-fold in hypertriglyceridemic persons (Figure 2). These results may not only allow one to define risk of atherosclerotic CAD more precisely, but may also have an impact on treatment decisions.

Strong support underscoring the importance of the triad of high triglycerides, low HDL cholesterol and elevated LDL cholesterol is provided by recent analysis of the Helsinki Heart Study.[20,21] Patients in the placebo group with triglyceride levels ≥200 mg/dl and an LDL cholesterol/HDL cholesterol ratio >5.0 had by far the highest incidence of cardiac events (relative risk 3.82 compared to those in the placebo group with triglyceride levels <200 mg/dl and an LDL cholesterol/HDL cholesterol ratio ≤5.0).[21] Treating patients with triglyceride levels ≥200 mg/dl and an LDL cholesterol/HDL cholesterol ratio >5.0 was particularly effective, reducing the incidence of cardiac events by >70%. These patients, encompassing 10% of the trial population, represented about 50% of CAD events saved with gemfibrozil.[20]

Conclusion: Taken together, the data from the PROCAM and the Helsinki Heart studies suggest that the hypertriglyceridemia/low HDL cholesterol syndrome constitutes a powerful risk factor for nonfatal myocardial infarction or CAD death that would escape attention if LDL cholesterol levels alone were determined. Apparently, when high triglyceride concentrations (≥200 mg/dl) coincide with a high ratio of plasma LDL cholesterol to HDL cholesterol (>5.0), steps should be taken to normalize the lipid profile. For practical purposes it appears advisable to base risk prediction for atherosclerotic CAD and treatment decision on a full lipid profile (cholesterol, triglycerides, LDL cholesterol, HDL cholesterol) rather than cholesterol or LDL cholesterol determinations alone.

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The Case for Unstable Angina Pectoris as a Primary End Point in Primary Prevention Studies

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Coronary artery disease (CAD) primary end point definitions used in previous prevention trials are reviewed, as well as trends over time for CAD mortality, incidence and hospital discharges to see if new primary end points should be considered. CAD mortality has shown a dramatic decline in the U.S. in the last 20 years, whereas the decrease in the incidence of acute myocardial infarction (AMI) is less consistent. The decline in CAD incidence and mortality has been attributed to changes in lifestyle and increased medical/surgical intervention. Hospital discharge rates for CAD have risen during the past decade. In addition, although the rate of discharge for AMI appears to have stabilized, the rates for angina, and more dramatically for unstable angina, have increased. Unstable angina made up 4% of CAD discharges in 1980, and increased to 25% of CAD discharges in 1989. Because of these trends, future trials that rely solely on AMI as a primary end point will not reflect the actual experience with CAD presentation in the U.S. Given the greater availability of methods to diagnose unstable angina more accurately, and because of its high risk pathology, it is concluded that unstable angina should receive serious consideration as a primary end point in future primary prevention trials.

(Am J Cardiol 1992;70:738–743)

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The opinions or assertions contained herein are the private views of the authors and are not to be construed as reflecting the views of the Department of Defense.

Coronary artery disease (CAD) is the leading cause of death and morbidity in the Western world. In 1987 in the U.S. alone, 513,000 people died of CAD, about 5,000,000 had CAD, and 1,500,000 new cases were reported.[1] In 1989 it was estimated that the cost of CAD in the U.S. was $41.5 billion. CAD can lead to various morbidity; the most important include acute myocardial infarction (AMI), congestive heart failure and angina pectoris.[2] The broadest definitions of angina are stable and unstable angina. The question addressed here is: Should additional CAD end points, namely unstable angina, be included as a primary end point in future CAD prevention trials to keep time and patient recruitment requirements realistic as well as obtain results that are reflective of current practice? To address this question, CAD primary end point definitions used in previous prevention trials are reviewed as well as trends for CAD mortality, incidence and hospital discharges.

REVIEW OF PUBLISHED REPORTS

The 2 most recently completed primary prevention trials are the Lipid Research Clinics — Coronary Primary Prevention Trial and the Helsinki Heart Study. The Lipid Research Clinic trial was begun in the 1970s and evaluated the efficacy of cholestyramine in reducing mortality and incidence of CAD in asymptomatic middle-aged men with primary hypercholesterolemia. Overall results showed the cholestyramine group experienced a 24% reduction in definite CAD death and a 19% reduction in nonfatal AMI.[3] In addition, beneficial effects were seen in other CAD-related events including coronary artery bypass graft surgery, angina pectoris and positive exercise test results. The Helsinki Heart Study used gemfibrozil to evaluate risk reduction of CAD in asymptomatic middle-aged men with primary dyslipidemia. There was a decrease in CAD incidence of 34% in the gemfibrozil group compared with the control group after 5 years of treatment.[4]

The Lipid Research Clinic trial defined as primary end points definite CAD death, definite nonfatal AMI, or both.[5] The Helsinki Heart Study used as primary end points: fatal AMI, possible AMI death, sudden cardiac death, unwitnessed death, and definite nonfatal AMI.[6] Both used similar routine electocardiographic criteria, history and laboratory evidence to define AMI.

Other prevention trials, including the Stockholm Ischemic Heart Disease Secondary Prevention Study,[7] the Oslo Study of the effects of diet and smoking intervention on CAD incidence,[8] and the Multiple Risk Fac-

tor Intervention Trial[9] used similar primary end points limited to fatal and nonfatal AMI. Each of these trials was performed before current diagnostic and therapeutic procedures were readily available.

TRENDS IN CORONARY ARTERY DISEASE MORTALITY, INCIDENCE AND HOSPITAL DISCHARGES

Over the last 20 years, there has been a consistent decline in CAD mortality in the U.S.[10] Whereas it is accepted that CAD mortality has decreased, declines in CAD incidence have been less dramatic.[11]

From 1968 to 1987, the age-adjusted CAD death rate in the U.S. declined by 40%, with greater relative decreases seen among younger patients.[12] A 43% decline in 10-year cardiovascular disease mortality was observed from 1950 to 1970 in Framingham,[13] a 55% decrease in CAD occurred in 35- to 44-year-old white men from 1970 to 1986 in Allegheny County,[14] and a 44% decrease in out-of-hospital mortality was observed in Worcester, Massachusetts between 1975 and 1981.[15]

Similarly, reductions have been seen in hospital case fatality rates. A 32% decline from 1975 to 1984 was seen in Worcester,[16] and declines were also seen in 24-hour and 30-day fatality for DuPont employees from 1957 to 1983.[17] Similar declines in CAD mortality have been observed in other westernized countries. Australia had a 40% decrease in in-hospital fatality over the last 20 years.[18] Italy showed 16 and 27% declines in in-hospital fatality for men and women, respectively, between 1976–1977 and 1983.[19] Most population studies also have shown a decrease in nonfatal CAD events. However, the reductions are neither as large nor as consistent as those seen for CAD mortality.[10] AMI was the exclusive condition used to characterize CAD in these studies and other major causes of CAD morbidity were not considered. In the Framingham Heart Study, using middle-aged white male cohorts identified between 1950 and 1970, 10-year CAD incidence for AMI, angina and sudden death decreased by 17% for men initially free from cardiovascular diseases, whereas baseline cardiovascular disease prevalence appeared to increase slightly.[13] A study conducted in Perth, Australia, between 1971 and 1982 showed that the incidence of AMI decreased by 24% in men and 37% in women, with those aged <45 years having nearly twice the relative decline of those aged ≥45 years.[20] Similarly, overall incidence of initial and recurrent AMI decreased by 27 and 22%, respectively, between 1975 and 1984 in Worcester.[16] Several other population studies show a net average decline in AMI incidence as early as 1969.[11,21]

Other studies have shown incidence changes in AMI that are variable among subgroups. In the DuPont study,[17] the decrease in incidence was higher among white-collar employees, and no decline was found in female employees. In the Worcester Heart Attack Study, the decline in incidence of AMI was 48% in those aged 25 to 44 years, and only 8% for those aged ≥75 years.[16] In the rural Pee Dee area of South Carolina, AMI incidence declined in white men aged 35 to 64 years; however, a sharp increase in incidence occurred for the 65- to 74-year-old cohort, suggesting a delay in onset of AMI.[22]

Two factors may have largely influenced CAD mortality and morbidity in the last 20 years: changes in lifestyle and earlier, more aggressive medical intervention.[23,24] Changes in lifestyle have reduced several primary risk factors including lower serum cholesterol, blood pressure control, and smoking cessation. Smoking cessation along with dietary modification may be the most important factors for this decline.[11,13,23–25] Goldman and others have suggested that a decrease in serum cholesterol by dietary changes and smoking cessation accounted for 54% of the CAD mortality decline from 1968 to 1976.[24] Greater relative reductions in AMI incidence and death rates have been seen in younger than in older populations. However, the fact that a greater overall decline has been seen in fatal versus nonfatal AMI indicates that the effect of reducing risk factors cannot be the only major factor.[26] If it were, the mortality decline would directly parallel a decline in overall CAD.[17]

Earlier recognition of symptoms by patients, more sensitive diagnostic procedures, and increased medical/surgical interventions also appear to be important factors in causing the decline in CAD mortality. Goldman and Cook[24] estimated that from 1968 to 1976, 40% of the decline in CAD mortality was due to medical interventions. This includes use of coronary care units, antihypertensive medication, prehospital resuscitation, coronary artery bypass surgery, and better medical treatment of CAD. From 1979 to 1986 the number of coronary artery bypass surgery procedures increased from 114,000/year to 228,000/year, and percutaneous transluminal coronary angioplasty increased from 2,000/year to 133,000/year.[27] From 1980 to 1984, a sevenfold increase was found in the use of bypass surgery or angioplasty, or both, for AMI.[28] Newer medical interventions include thrombolytic therapy, potent cholesterol-lowering drugs, β blockers and calcium antagonists.

Whereas the decreased mortality and incidence would be expected to decrease the rate of hospitalization for CAD substantially, such has not been the case. In Massachusetts, while a 4% decrease in CAD mortality was found between 1980 and 1984, hospital discharges for CAD increased by 17% in the same period.[28] Similarly, an increase from 1,161,000 to 1,323,000 primary discharges for CAD was found for U.S. men between 1984 and 1986.[27]

Several factors may be involved in producing this apparent discrepancy between the increasing hospital discharge rates and decreasing mortality and incidence. These include earlier disease recognition, increased diagnostic sensitivity and decreased fatality.[22,29] The first 2 factors would increase the number of people admitted for newly diagnosed disease, while the latter would increase the number of readmissions. The trends over time in hospital discharges for CAD were examined to see if the increases observed[27] were consistent across diagnoses.

TABLE I Age-Sex Specific Discharges for Primary Diagnosis of Myocardial Infarction (ICD9 410)—1980, 1985, 1986, 1987, 1988, 1989

	Year of Discharge					
Age (yr)	1980 No.*(rate/1,000)	1985 No.*(rate/1,000)	1986 No.*(rate/1,000)	1987 No.*(rate/1,000)	1988 No.*(rate/1,000)	1989 No.*(rate/1,000)
Men						
0–54	67.8 (.76)	114.8 (1.22)	108.6 (1.15)	119.2 (1.26)	103.8 (1.09)	104.3 (1.09)
55–69	134.8 (9.60)	206.6 (14.00)	204.3 (13.78)	212.5 (14.30)	197.3 (13.30)	187.9 (12.67)
70+	69.5 (10.86)	144.4 (19.83)	153.4 (20.60)	146.1 (20.60)	149.8 (19.19)	128.7 (16.48)
Women						
0–54	15.5 (.17)	30.0 (.32)	23.7 (.25)	29.9 (.31)	26.0 (0.27)	28.0 (0.29)
55–69	62.4 (3.80)	96.9 (5.70)	108.4 (6.35)	98.4 (5.77)	91.2 (5.37)	91.0 (5.35)
70+	81.3 (7.85)	161.8 (13.69)	157.7 (13.07)	153.7 (12.47)	148.2 (11.79)	155.0 (12.33)
All age/sex†	431.5 (1.96)	754.5 (3.19)	756.1 (3.16)	759.8 (3.14)	716.4 (2.94)	694.9 (2.85)

*In thousands of discharges, includes both first and recurrent events.
†Rates are age-sex adjusted to the 1989 population.

METHODS

Data were evaluated from the National Hospital Discharge Survey for the years 1980, 1985, 1986, 1987, 1988 and 1989 to obtain discharges for all CAD diagnoses as well as computation of CAD discharge rates. These data do not distinguish between discharges for initial versus recurrent events. The survey is continuous and conducted by the National Center for Health Statistics. The survey provides estimates of total hospitalizations, with information on up to 7 different diagnoses and 4 surgical procedures per discharge.[30] Discharge diagnoses were coded centrally based on the *International Classification of Diseases, 9th Revision, Clinical Modification.* The estimates are based on a probability sample of U.S. nonfederal short-stay hospitals and are generalizable to all such hospitals in the U.S.

National discharge and rate estimates are given for first-listed diagnoses of the code cited, having been calculated from the sample cases using National Center for Health Statistics specified weights. Discharges for AMI, post-AMI syndrome, unstable angina pectoris, other acute coronary insufficiency and ischemia, angina pectoris, coronary atherosclerosis and cardiovascular arteriosclerosis were used to define CAD discharges and were divided according to sex and age (<55 years, 55 to 69, 70+). The total number of estimated discharges for a diagnosis was then divided by the U.S. population for the appropriate age group in the specified year to arrive at a discharge rate. Population statistics were based on data derived from census estimates for the corresponding years.

RESULTS

For all diagnoses combined, the total number of CAD discharges increased from 1.9 million in 1980 to 2.2 million in 1987 (+16%), with a decrease to 2 million in 1989 (Figure 1). Post-AMI syndrome, acute coronary insufficiency and ischemia and cardiovascular arteriosclerosis each accounted for <6% of CAD discharges in each year, and remained stable or decreased over time and are not considered further (see Figure 1). The most frequent discharge diagnosis in each year was AMI, increasing from 431,000 in 1980 to 760,000 in 1987, with a decrease to 695,000 in 1989 (Table I). Age-sex specific rates of discharges for AMI showed similar trends over time, with peak rates in the mid-1980s and thereafter declining. In 1989, the rate of discharge for AMI for 55- to 69-year-old men (12.7/

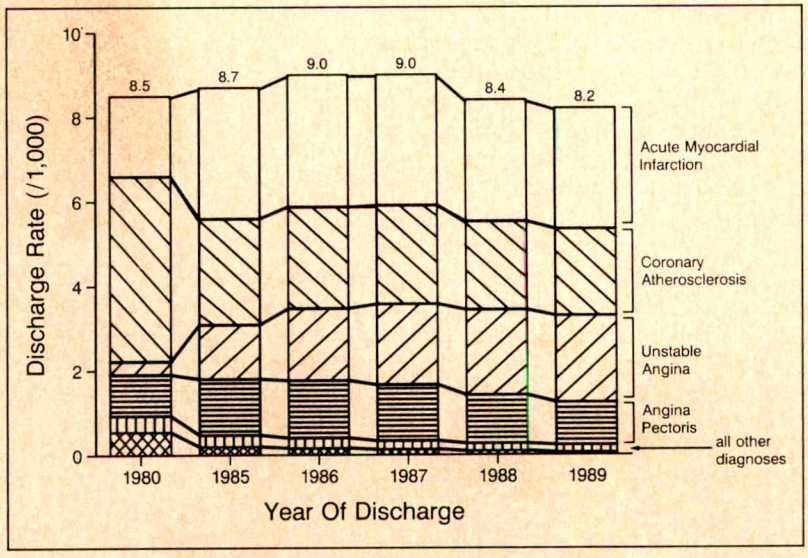


FIGURE 1. National Hospital Discharge Survey — discharge rates for coronary heart disease in the U.S. 1980 and 1985 to 1989. The total height for each *bar* represents the age-adjusted discharge rate for all coronary artery diseases. The height of each *shaded portion* represents the rate for each diagnosis. The *cross-hatched bars* are for all other coronary artery disease diagnoses including post-acute myocardial infarction syndrome (not visible due to low incidence), acute coronary insufficiency and ischemia *(wide cross-hatch)* and cardiovascular arteriosclerosis *(narrow cross-hatch).*

1,000) was 2.4 times that in women. This male/female ratio decreased to 1.3 in those aged >70 years.

The second most frequent diagnosis was coronary atherosclerosis, accounting for 51% of CAD discharges in 1980 (Table II). However, the frequency of this nonspecific diagnosis declined consistently in all age-sex groups, and by 1989 accounted for 25% of CAD discharges.

Unstable (Table III) and stable (Table IV) angina accounted for 15% of CAD discharges in 1980. Both increased in frequency of discharge, accounting for 37% of CAD discharges in 1989. Unstable angina showed a consistent and dramatic increase in discharges, increasing from 71,000 in 1980 to 498,000 in 1989. Like AMI, the discharge rate for unstable angina increased with age for both sexes.

DISCUSSION

One factor that undoubtedly accounts in part for the observations from the National Hospital Discharge Survey data is the effect of government reimbursement policies for hospital care based on discharge diagnosis.

TABLE II Age-Sex Specific Discharges for Primary Diagnosis of Coronary Atherosclerosis (ICD9 414)—1980, 1985, 1986, 1987, 1988, 1989

	Year of Discharge					
Age (yr)	1980 No.*(rate/1,000)	1985 No.*(rate/1,000)	1986 No.*(rate/1,000)	1987 No.*(rate/1,000)	1988 No.*(rate/1,000)	1989 No.*(rate/1,000)
Men						
0–54	151.7 (1.69)	109.4 (1.16)	99.6 (1.06)	91.9 (0.97)	89.6 (0.94)	90.0 (0.94)
55–69	263.7 (18.76)	191.5 (12.98)	194.6 (13.12)	192.6 (12.96)	182.5 (12.30)	184.7 (12.45)
70+	150.5 (23.51)	74.8 (10.28)	77.6 (10.42)	82.9 (10.87)	71.9 (9.21)	69.3 (8.88)
Women						
0–54	51.2 (0.57)	25.3 (0.27)	30.3 (0.32)	32.0 (0.34)	24.1 (0.25)	23.2 (0.24)
55–69	134.3 (8.17)	89.8 (5.28)	93.7 (5.49)	90.6 (5.31)	75.2 (4.43)	75.7 (4.46)
70+	205.9 (19.86)	92.0 (7.78)	80.5 (6.67)	69.9 (5.67)	67.5 (5.37)	58.3 (4.64)
All age/sex†	957.2 (4.37)	582.9 (2.45)	576.3 (2.40)	560.0 (2.31)	510.8 (2.09)	501.3 (2.05)

*In thousands of discharges, includes both first and recurrent events.
†Rates are age-sex adjusted to the 1989 population.

TABLE III Age-Sex Specific Discharges for Primary Diagnosis of Unstable Angina (ICD9 411.1)—1980, 1985, 1986, 1987, 1988, 1989

	Year of Discharge					
Age (yr)	1980 No.*(rate/1,000)	1985 No.*(rate/1,000)	1986 No.*(rate/1,000)	1987 No.*(rate/1,000)	1988 No.*(rate/1,000)	1989 No.*(rate/1,000)
Men						
0–54	9.6 (0.11)	44.8 (0.48)	46.1 (0.49)	49.2 (0.52)	58.4 (0.61)	57.1 (0.60)
55–69	18.7 (1.33)	70.7 (4.79)	89.6 (6.04)	103.9 (6.99)	123.9 (8.35)	118.9 (8.02)
70+	8.0 (1.26)	46.8 (6.43)	72.5 (9.74)	70.7 (9.28)	77.8 (9.96)	79.3 (10.16)
Women						
0–54	5.0 (0.06)	16.2 (0.17)	27.9 (0.30)	28.3 (0.30)	31.9 (0.33)	33.6 (0.35)
55–69	15.4 (0.94)	69.0 (4.06)	74.7 (4.38)	90.1 (5.28)	82.2 (4.84)	92.5 (5.45)
70+	14.3 (1.38)	68.2 (5.76)	97.6 (8.09)	116.3 (9.44)	113.4 (9.02)	116.5 (9.27)
All age/sex†	71.0 (0.32)	315.6 (1.33)	408.6 (1.71)	458.6 (1.90)	487.6 (2.00)	498.0 (2.04)

*In thousands of discharges, includes both first and recurrent events.
†Rates are age-sex adjusted to the 1989 population.

TABLE IV Age-Sex Specific Discharges for Primary Diagnosis of Angina Pectoris (ICD9 413)—1980, 1985, 1986, 1987, 1988, 1989

	Year of Discharge					
Age (yr)	1980 No.*(rate/1,000)	1985 No.*(rate/1,000)	1986 No.*(rate/1,000)	1987 No.*(rate/1,000)	1988 No.*(rate/1,000)	1989 No.*(rate/1,000)
Men						
0–54	40.4 (0.45)	51.4 (0.55)	47.7 (0.51)	46.5 (0.49)	37.0 (0.39)	33.8 (0.35)
55–69	48.0 (3.41)	64.1 (4.35)	75.6 (5.10)	76.9 (5.17)	64.1 (4.32)	54.5 (3.68)
70+	26.2 (4.10)	41.1 (5.64)	39.9 (5.36)	42.3 (5.54)	34.6 (4.43)	34.4 (4.41)
Women						
0–54	26.1 (0.29)	31.1 (0.33)	25.0 (0.26)	30.5 (0.32)	31.5 (0.33)	20.6 (0.21)
55–69	46.4 (2.82)	57.9 (3.40)	57.6 (3.38)	61.2 (3.59)	48.3 (2.84)	45.6 (2.68)
70+	26.3 (2.53)	68.2 (5.76)	72.7 (6.03)	63.8 (5.17)	63.9 (5.08)	56.4 (4.49)
All age/sex†	213.4 (0.96)	313.7 (1.32)	318.6 (1.33)	321.1 (1.33)	279.3 (1.15)	245.3 (1.00)

*In thousands of discharges, includes both first and recurrent events.
†Rates are age-sex adjusted to the 1989 population.

Since 1984, reimbursement has been based on prospective payments per case according to diagnostic-related groups. Under this system, there is possibly incentive to diagnose in a category with more days allowed (AMI and unstable angina) and not use more poorly paid codes. Possibly, additional incentives to perform procedures might reduce the length of stay per case, while increasing total admissions and reducing duration per stay.

Nevertheless, angina pectoris, with one of the shortest allowable lengths of stay (5.0 days, Wood D, personal communication, HCFA Medicine Statistics Office, Hyattsville, Maryland, August 1990), had an increase in total discharges of 50%, suggesting that reimbursement policies are not the only factor affecting discharge rates. The increase may also reflect a greater tendency to hospitalize patients presenting with chest pain.

In 1980, the categories of stable and unstable angina accounted for only 15% of the total CAD discharges, whereas in 1989 they accounted for 37% of CAD discharges. Although AMI also increased from 23% of total discharges in 1980 to 35% in 1989, its increase was not as great in either relative or absolute terms as that reported for stable and unstable angina. The shift in CAD hospitalizations away from AMI toward less severe ischemic events may be due to earlier recognition, diagnosis and medical intervention.

COMMENTS

CAD mortality has declined and CAD incidence, as indicated by AMI incidence, has probably decreased to a lesser extent, whereas overall CAD discharges have increased and apparently peaked in recent years. The reasons for the mortality and incidence declines are most likely a decrease in risk factors, earlier disease recognition and increased medical intervention. The increase in total discharges may also be due in part to these factors as well as increased AMI survival with resulting recurrent CAD hospitalizations.

The CAD primary end points in past primary prevention trials, which were based on AMI and CAD death alone, excluded from consideration the actual presentation seen in current clinical practice.

The fact that unstable and stable angina accounted for more hospital discharges in 1989 than AMI makes a strong case for including angina as a primary end point in CAD primary prevention trials. Because of earlier and more aggressive interventions, it is reasonable to assume that such patients often have an AMI postponed for several years, in many cases beyond the duration of follow-up in a primary prevention trial.

Of tantamount consideration for the inclusion of angina as a primary end point is whether or not the different anginal states represent an atherogenic process that is similar to AMI. It has been shown that patients with stable angina are less likely to have plaque ulceration, occlusive thrombus or eccentric obstructions than patients with recent-onset angina at rest or with minimal exertion.[31-33] Thus, stable angina may in part represent a different pathologic process and should probably not be considered as a primary end point. Whereas clinical history alone is insufficient for the diagnosis of unstable angina, all coronary syndromes are more accurately diagnosed today. Thus, a study that included unstable angina as a primary end point would need appropriate diagnostic procedures performed to confirm the diagnoses.

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Asymptomatic Cardiac Ischemia Pilot Study (ACIP)

The ACIP Investigators*

Ischemia can lead to myocardial necrosis, arrhythmias and death. Current practice suggests that asymptomatic or silent myocardial ischemia be treated as though it were symptomatic ischemia. This practice is associated with a growing trend of more frequent use of electrocardiographic monitoring, more complex therapeutic drug regimens and more frequent use of revascularization. However, there is no adequate study of the efficacy and safety of alternative therapeutic approaches to the treatment of asymptomatic myocardial ischemia. Therefore, the National Heart, Lung, and Blood Institute has planned the Asymptomatic Cardiac Ischemia Pilot (ACIP) study. The ACIP study is a multicenter international pilot trial to determine the efficacy and safety of angina-directed medical therapy, angina plus ambulatory electrocardiographic-directed medical therapy and revascularization. The treatment of asymptomatic cardiac ischemia is double-blind and placebo-controlled. The primary end point is elimination of ischemia on the 48-hour electrocardiogram at 12 weeks. Patients will be followed-up for at least 1 year. Secondary analyses will include comparisons of the 2 medical regimens, amounts of medicine taken, and exercise versus electrocardiographic results. Eleven clinical units are recruiting 600 patients with coronary anatomy suitable for revascularization, a positive exercise stress test, and 1 or more asymptomatic ischemic episodes on the 48-hours electrocardiogram. Patients are stratified by center, symptom status and previous coronary surgery. If warranted by the pilot study results, a full-scale trial will be considered to determine whether amelioration of asymptomatic ischemia improves survival and reduces cardiovascular morbidity.

(Am J Cardiol 1992;70:744–747)

From the Cardiac Diseases Branch, Division of Heart and Vascular Diseases, National Heart, Lung, and Blood Institute, Bethesda, Maryland. This study was supported by research contracts HV-90-07, HV-90-08, HV-91-04, HV-91-05 and HV-91-14 from the National Heart, Lung, and Blood Institute, Bethesda, Maryland. Manuscript received April 9, 1992; revised manuscript received May 26, 1992, and accepted May 27.

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*The investigators and centers participating in the ACIP trial are listed in the Appendix.

Patients with stable coronary artery disease (CAD) frequently have cardiac ischemia during routine ambulatory activities. Most of these ischemic events are asymptomatic. Observational studies indicate that the presence of ischemia is associated with an adverse cardiac prognosis. The Asymptomatic Cardiac Ischemia Pilot (ACIP) study is a multicenter international trial funded by the National Heart, Lung, and Blood Institute (NHLBI) comparing the relative efficacy of 3 randomly assigned therapeutic strategies for suppression of ischemia assessed by a 48-hour ambulatory electrocardiography. The 3 strategies are (1) angina-guided therapy with incremental levels of anti-ischemic medication to relieve angina; (2) angina-guided plus ambulatory electrocardiographic-guided therapy with incremental levels of anti-ischemic medication to relieve angina and to eliminate ischemia on a 48-hour ambulatory electrocardiogram (ECG); and (3) revascularization of all important stenoses in major coronary arteries. The study will assess the feasibility of, and establish the methods for a full-scale clinical trial of therapies to prevent clinically important events (e.g., death, myocardial infarction) among patients with myocardial ischemia, with or without angina.

Objectives: One of the primary objectives of the pilot study is to determine the relative efficacy of the 3 therapies in providing freedom from myocardial ischemia. For that purpose, the principal end point is evidence of myocardial ischemia, defined as ≥1 mm of ST-segment depression lasting for at least 1 minute, on a 48-hour ambulatory ECG at 12 weeks after study enrollment. By that time patients randomized to either medical treatment strategy will have completed medication adjustments and patients randomized to revascularization will have undergone the procedures. Other objectives are to confirm the frequency of asymptomatic cardiac ischemia among symptomatic and asymptomatic patients and to clarify other issues important for a full-scale clinical trial. These include compliance with assigned therapies, availability of patients for randomization, and estimates of mortality and rates of nonfatal cardiovascular events.

Patient selection: Men and women must have (1) at least 1 coronary artery narrowing of ≥50% luminal diameter, as measured with calipers, in a major vessel suitable for revascularization; (2) objective evidence of stress-related ischemia, such as abnormal exercise stress ECG; and (3) at least 1 episode of asymptomatic ischemia on a 48-hour ambulatory ECG.

Randomization: Randomization is stratified by the following: clinical unit and whether the patient at the time of study entry is symptomatic or asymptomatic, or has had coronary artery bypass surgery. Eligible partici-

pants will be assigned equally to the 3 treatment groups (Figure 1).

Treatment strategies: After randomization, patients in 2 medical groups undergo an initial period of open medication titration to control angina. After a 4-week open label period an ambulatory ECG is obtained to guide therapy in a double-blind manner to control remaining ischemia. Regardless of the presence or absence of asymptomatic ischemia, therapy to control angina will be adjusted throughout the study in an unblinded manner.

For patients in 1 of the 2 medical groups the treatment sequence used to suppress asymptomatic ischemia, detected by ambulatory ECG, is the same as that used for angina, except that it will be administered in a double-blind fashion, i.e., neither the study physician nor the participant is able to distinguish angina-guided therapy from angina-guided plus ambulatory electrocardiographic guided therapy on the basis of study medications. This is accomplished by identical packaging of active study medication and placebo. Patients assigned to angina-guided therapy receive additional placebo if their ambulatory ECG shows ischemic episodes, and those assigned to angina plus ambulatory electrocardiographic-guided therapy receive additional anti-ischemic drug. Two medication sequences are used. For patients who must take a β blocker, therapy is begun with atenolol; those who cannot take a β blocker are given diltiazem; and those who can take either medication are randomized to 1 or the other of these initial drugs. Stepped therapy consists either of 2 incremental levels of atenolol to be followed by 2 levels of nifedipine or 2 levels of diltiazem to be followed by 2 levels of isosorbide dinitrate. All patients will be advised to take 325 mg/day of aspirin.

Patients assigned to revascularization undergo coronary angioplasty or coronary artery bypass surgery, whichever is appropriate. In addition to revascularization, these patients are treated with open-label medications using the same regimens to control angina as those in patients assigned to medical therapy.

Data collection: Patients will undergo 48-hour ambulatory electrocardiography before study entry (baseline), and at 12 weeks, 6 months and 1 year after study entry. Patients in the 2 medical groups will also undergo ambulatory electrocardiography at 4 and 8 weeks after study entry to titrate the medications. An exercise tolerance test will be performed at baseline, 12 weeks, 6 months and 1 year after study entry. Major clinical events (e.g., death, myocardial infarction, hospitalization for unstable angina) will be ascertained at the time of each follow-up. Anginal status will be ascertained by a standard questionnaire at baseline, 12-weeks, 6 months, 9 months and 1 year. All patients will be monitored for at least 1 year after enrollment.

Sample size: The overall recruitment goal for the ACIP study is 600 patients with 200 patients in each of the 3 treatment groups. The statistical power to detect differences in the proportion of patients with ischemia present on ambulatory ECG among the 3 groups has

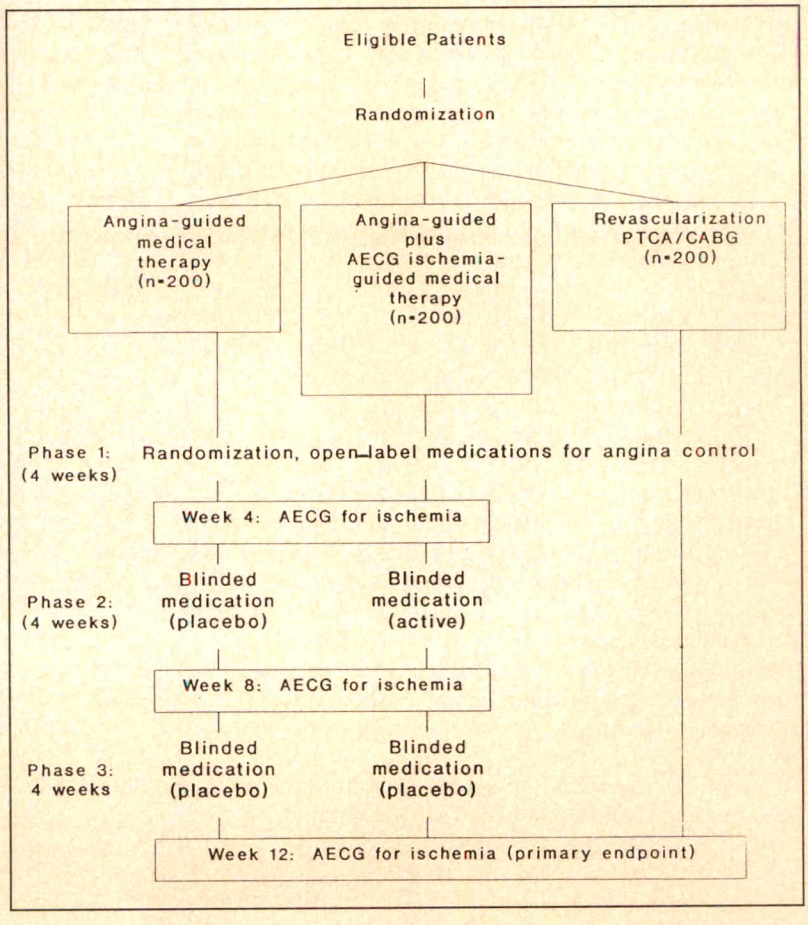


FIGURE 1. The Asymptomatic Cardiac Ischemia Pilot study design. AECG = ambulatory electrocardiogram; CABG = coronary artery bypass grafting; PTCA = percutaneous transluminal coronary angioplasty.

been calculated for pairwise comparisons. Since there are 3 pairwise tests, the α level will be adjusted for multiple comparisons. Because this is a pilot study, an overall α of 0.10 will be used. The power to detect a 50% reduction in the proportion of patients with ischemia in the comparison group depends on the number of patients assigned to each treatment group, the proportion of patients with ischemia in the group with more ischemia, and the α level of the test. For example, if the number of patients in each treatment group is 200, and the proportion of patients with ischemia present on ambulatory ECG is 0.30 (30%) with 1 treatment, then a test of differences in proportions at $\alpha = 0.10/3 = 0.033$ will have power equal to 0.93 to distinguish the effect of another treatment which is associated with a proportion of patients with ischemia of 0.15 (15%). Because some patients may be lost to follow-up, some may have uninterpretable ambulatory ECGs, and some may not comply with assigned therapies. An effective treatment group size of 10% less than that actually enrolled and assigned has been specified to estimate power. For 180 "effective" patients in each treatment group, the power of this comparison is 0.90.

Organizational structure: The primary governing body of ACIP is the Steering Committee, which consists of principal investigators from each clinical unit, the core laboratories, the clinical coordinating center, the research pharmacy center, together with the study chairman and the NHLBI project officer. The committee provides the scientific direction for the study. A smaller operation committee monitors the study progress weekly and resolves any issues related to day-to-day operations. The Biostatistics Research Branch of the NHLBI provides additional statistical expertise in the design and analysis of the study. Specific primary and secondary end points and other relevant information concerning potential adverse and beneficial effects of each of the assigned therapies will be reviewed regularly by the Data and Safety Monitoring Board to determine whether any protocol changes are warranted because of evidence of adverse effects in 1 or more treatment groups. The Mortality and Morbidity Classification Committee will review and classify fatal and nonfatal coronary events using predetermined definitions.

Data analysis: Primary analyses will be based on intention to treat: All patients will be analyzed by the treatment randomly assigned. Treatments will be compared using pairwise tests of the proportion of patients with ischemia on the 12-week ambulatory ECG. In addition, a selected number of relevant subgroup analyses will be done using baseline characteristics. Secondary analyses will include comparisons of the 2 medical regimens, amounts of drugs taken and exercise versus ambulatory electrocardiographic results. Data will be collected and analyzed by the clinical coordinating center.

Core laboratories: Three core laboratories have been established to uniformly process ambulatory ECGs, rest and exercise ECGs, and coronary angiograms.

Other research studies related to the Asymptomatic Cardiac Ischemia Pilot Study: The Psychophysiological Investigation of Myocardial Ischemia (PIMI) study will evaluate neurologic and psychophysiologic characteristics related to the manifestation and presentation of symptomatic and asymptomatic cardiac ischemia. Approximately 225 patients will be recruited from 4 participating ACIP clinical units.

APPENDIX

List of participating clinical units, core laboratories and coordinating center: ACIP clinical units: *University of Alabama at Birmingham:* W.J. Rogers, MD,* K. Al-Shaibi, MD, V. Bitner, MD, G. Blackburn, LPN, D. Cox, MD, L. Levson, RN, L. McDaniel, RN, J. Moody, RN, T. Morgan, RN, M. Parks, MD, H. Taylor, MD, V. Varma, MD. *Baylor College of Medicine:* C. Pratt, MD,* M. Francis, RN, G. Habib, MD, S. Johnson, N. Kleiman, MD, J. Mahmarian, MD, G. Morris, RN, R. Roberts, MD, R. Rodriguez, RN, B. Stein, MD, C. Thibedeaux. *Brigham and Women's Hospital:* A.P. Selwyn, MD,* J. Barry, RN, K. Raby, MD, P. Stone, MD, G. Vita, RN, A. Young, MD. *University of Florida and VAMC:* C.J. Pepine, MD,* J. Alexander, MD, B. Bertolet, MD, E. Handberg, RN, J. Hill, MD, R. Kolb, RN, M. Limacher, MD, J. Mehta, MD, G. Ruby, RN. *Henry Ford Hospital:* A.D. Goldberg, MD,* L. Dvorak, RN, D. Frank, RN, S. Goldstein, MD, S. Jafri, MD, PhD, K. Knight, RN, Kraft, RN. *Johns Hopkins University:* P. Ouyang, MD,* S. Achuff, MD, K. Baughman, MD, J. Brinker, MD, S.O. Gottlieb, MD, S. Gottlieb, MD, G. Groman, MD, M. Kelemen, MD, H. Lutz, RN, S. Schulman, MD, S. Townsend, RN. *Albert Einstein College of Medicine:* H. Mueller, MD,* S. Bilodeau, RN, M.E. Coglianese, RN, M. Fornaiser-Bongo, BS, W. Frishman, MD, S. Furia, RN, K. Hemingway, RN, R. Steingart, MD, B. Ventura, RN. *Montreal Heart Institute:* M.G. Bourassa, MD,* R. Bonan, MD, I. Dyrda, MD, C. Faille, Y. LeClerc, MD, J. Lespérance, MD, C. Pelletier, MD, J. Trudel, RN, D.D. Waters, MD, L. Whittom, RN. *University of Ottawa Heart Institute:* R.F. Davies, MD,* M. Baird, MD, D. Beanlands, MD, A. Baker, RN, M. Fraser, RN, S. Grichen. *St. Bartholomew's Hospital, London, U.K.:* J.E. Deanfield, MD,* D. Dymond, MD, J. Elstob, RN. *St. Louis University Medical Center and VAMC:* B.R. Chaitman, MD,* P. Bjerregaard, MD, S. Byers, RN, D.G. Caralis, MD, MPH, J. Cohen, MD, G. Kaiser, MD, M. Kern, MD, L. McBride, MD, D.D. Miller, MD, R.D. Wiens, MD, G. Williams, MD.

PIMI clinical units: *University of Alabama at Birmingham:* J. Raczynski, PhD,* C. Coghlan, MD, H. Taylor, MD. *University of Florida:* C. Pepine, MD,* B. Bertolet, MD, A. Greene, PhD, E. Handberg, RN, E. Johnson, PhD, L. Lindholm, MS, M. Robinson, PhD. *St. Louis University:* J. Cohen, MD,* R. Carney, PhD, K. Freedland, PhD. *Henry Ford Hospital:* M. Ketterer, PhD,* B.K. Ahmad, MD, A.D. Goldberg, MD.

*Principal Investigator.

Clinical coordinating center: *Maryland Medical Research Institute:* G. Knatterud, PhD,* S. Forman, MA, C. Kelly, D. Krantz, PhD, W. Maixner, PhD, R. McMahon, PhD, E. Mirenzi, P. Noble, M.L. Terrin, MD, MPH.

Ambulatory electrocardiography core laboratory: *Brigham and Women's Hospital:* P. Stone, MD,* T. Andrews, MD, G. MacCallum.

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*Principal Investigator.

Biochemistry core laboratory (for PIMI) (to be selected).

Radionuclide core laboratory (for PIMI) (to be selected).

Research pharmacy coordinating center: Philip Day, RPh, MS,* J. Overfelt, L. Richards, M. Sather, RPh, MS.

ACIP Study Chairman: C.R. Conti, MD, University of Florida, Gainesville.

PIMI Study Chairman: D. Sheps, MD, University of North Carolina.

Project Office: *Cardiac Diseases Branch, Division of Heart and Vascular Diseases and Behavioral Medicine Branch, Division of Epidemiology and Clinical Applications, National Heart, Lung, and Blood Institute:* G. Sopko, MD, MPH (ACIP Project Officer), P. Kaufmann, PhD (PIMI Project Officer), K. Camiletti, D. Frye, N. Geller, PhD, M. Horan, MD, S. Kraft, M. Proschan, PhD.

Long-Term Prognostic Significance of Ambulatory Electrocardiographic Findings in Apparently Healthy Subjects ≥60 Years of Age

Jerome L. Fleg, MD, and Harold L. Kennedy, MD, MPH

To determine the long-term prognostic significance of frequent or complex ectopic beats and ST-segment changes on 24-hour ambulatory electrocardiogram (ECG) in apparently healthy older subjects, 98 volunteers were followed up from the Baltimore Longitudinal Study of Aging who were 60 to 85 years old and free of cardiac disease by history, physical examination and maximal treadmill testing at the time of ambulatory ECG between 1978 and 1980. Over a mean follow-up period of 10 years, coronary events developed in 14 subjects: angina pectoris in 7, nonfatal myocardial infarction in 3 and sudden cardiac death in 4. The incidence of coronary events did not differ significantly between subjects who developed the following arrhythmias and those who did not, respectively: ≥30 supraventricular ectopic beats in any hour, 18 vs 13%; ≥100 supraventricular ectopic beats in 24 hours, 20 vs 12%; paroxysmal atrial tachycardia, 15 vs 14%; ≥30 ventricular ectopic complexes (VECs) in any hour, 17 vs 14%; ≥100 VECs in 24 hours, 18 vs 14%; or repetitive VECs, 20 vs 13%. The mean 24-hour heart rate (75 ± 8 vs 72 ± 9 beats/min) as well as the maximal (116 ± 20 vs 111 ± 18 beats/min) and minimal (51 ± 6 vs 53 ± 7 beats/min) heart rate also did not differ between the coronary event and non-event groups. Although flat or downsloping ST-segment depression ≥1.0 mm was seen in only 5 subjects, coronary events occurred in 2 of these 5 (40%) vs only 12 (13%) of 93 subjects without such ST-segment changes. When 11 additional persons with lesser degrees of ST-segment depression were included, events occurred in 6 of 16 (38%) compared with 8 of 82 (10%) subjects without any ST-segment changes, $p < 0.05$. In 2 of the 3 subjects who died suddenly, both nonsustained ventricular tachycardia and ST-segment depression were present. Thus, neither supraventricular ectopic beats nor simple VEC patterns on ambulatory ECG predict the development of future coronary events in clinically healthy older subjects; ambulant silent ischemia, although infrequent, may be the best predictor of future coronary events in such a population.

(Am J Cardiol 1992;70:748–751)

It is well established that both the prevalence and complexity of ventricular ectopic complexes (VECs) increases with age in apparently healthy persons.[1–3] In patients with organic heart disease, the density and complexity of VECs on ambulatory electrocardiogram (ECG) are independent predictors of cardiac mortality.[4,5] Although frequent and complex ambulatory VECs in apparently healthy younger persons are not associated with an adverse outcome,[6] whether ambulatory VEC patterns have prognostic importance in apparently healthy older subjects is controversial. In ambulatory subjects aged >75 years, those with >10 VECs/hour had approximately double the mortality of those with less frequent VECs over 5 years of follow-up.[7] However, frequent or repetitive VECs on ambulatory ECG did not predict increased cardiac mortality in institutionalized elderly patients without apparent heart disease.[8] The prognostic significance of frequent or complex supraventricular ectopic beats in apparently healthy subjects has not been investigated. Recent studies have documented increased coronary event rates in patients with known coronary artery disease who demonstrate ischemic ST segments during 24-hour electrocardiographic recording.[9–11] The importance of such electrocardiographic changes in asymptomatic persons is not known. The present study was designed to determine the long-term significance of frequent or complex VECs, supraventricular ectopic beats, and ST-segment changes observed during 24-hour ambulatory electrocardiography in 98 apparently healthy older volunteers from the Baltimore Longitudinal Study of Aging, followed prospectively for an average of 10 years.[12]

METHODS

Between July 1978 and March 1980, 24-hour ambulatory ECGs were recorded in 101 asymptomatic participants in the Baltimore Longitudinal Study on Aging who were aged ≥60 years and fulfilled the following additional criteria[12]: (1) no history of cardiac symptoms or disease and no evidence of systemic illness; (2) normal findings on cardiac physical examination; (3) resting blood pressure <160/95 mm Hg; (4) normal heart and lungs on chest x-ray examination; (5) no evidence of prior myocardial infarction, codable ST-segment ab-

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normality (Minnesota code 4:1, 4:2, 4:3, or 4:4),[12] atrial enlargement, ventricular hypertrophy or bundle branch block on 12-lead resting ECG; (6) normal spirometry results; (7) normal response to maximal exercise treadmill test (Balke protocol); and (8) no medication that might affect cardiac rate or rhythm. Holter recordings from 3 subjects were technically unsatisfactory; these subjects were excluded from the analysis, leaving a study population of 98.

Twenty-four-hour ambulatory electrocardiography was performed with either a Del Mar Avionics model 445 or 447, or a Marquette model 5300 recorder, using bipolar leads V_1 and V_5. All of these recorders have an adequate frequency response (0.07 to 100 Hz). Before leaving the laboratory, each subject was given a diary and instructed to record all symptoms and activities. During the entire 24-hour period, subjects were housed in a self-care hospital ward. Between 8 A.M. and 5 P.M. they underwent a wide variety of noninvasive tests assessing pulmonary function, intelligence and personality, vision and hearing, basal metabolism and glucose tolerance. All subjects were ambulatory and without restriction on physical activities after testing hours. Holter recordings were analyzed on a Del Mar Avionics Electroscanner 660 for cardiac arrhythmias. Subsequently, the tapes were reanalyzed on a Del Mar 750A instrument system for confirmation of cardiac arrhythmias and assessment of ST-segment changes. ST-segment changes were reported when positional changes were excluded, and the ST-segment J point deviated >1 mm from baseline recordings for at least 1 minute. The ST-segment response was considered ischemic if horizontal or downsloping at 80 ms beyond the J point (Minnesota code 4:1) and nondiagnostic if the ST segment was slowly upsloping (code 4:4).[13]

Subjects were evaluated during their subsequent biennial visits to the Gerontology Research Center for the development of new coronary events: (1) angina pectoris, defined by a positive response to the Rose anginal questionnaire and confirmed by interview with a trained technician unaware of the ambulatory ECG result; and (2) myocardial infarction, defined by a hospital record that confirmed infarction or by development of new Q waves (Minnesota code 1:1 or 1:2 on resting ECG). For persons who died over the follow-up period, cause of death was determined from autopsy reports, hospital or physician records and death certificates. A cardiac death was defined as death from acute myocardial infarction or sudden cardiac death. Follow-up information was obtained on all subjects.

For each of the following arrhythmia categories, the incidence of coronary events was compared between the group with and the group without the given arrhythmia: ≥30 supraventricular ectopic beats in any hour, ≥100 in 24 hours, paroxysmal supraventricular tachycardia, ≥30 VECs in any hour, ≥100 VECs in 24 hours, and ventricular couplets or ventricular tachycardia. In addition, the coronary event rate for those exhibiting transient ST-segment depression was compared with that for the group without such ST changes. Event-free survival rates in these 2 groups were compared by Kaplan-Meier survival analysis. The resulting curves were compared by the log-rank statistic. The maximal, minimal and mean heart rates were compared between the subjects who did and did not have an event. Continuous variables are shown as mean ± SD. Comparisons were obtained by chi-square analysis with Yates correction, Fisher's exact test or by unpaired *t* test as appropriate; a 2-tailed p value ≤0.05 indicated statistical significance.

TABLE I Arrhythmia Prevalence in 98 Older Volunteers

Arrhythmia	Prevalence (%)
Supraventricular	
≥30 supraventricular ectopic beats in any hour	22
≥100 supraventricular ectopic beats in 24 hours	26
Paroxysmal supraventricular tachycardia	13
Ventricular	
≥10 VECs in any hour	29
≥30 VECs in any hour	12
≥100 VECs in 24 hours	17
Couplets or nonsustained VT	15

VECs = ventricular ectopic complexes; VT = ventricular tachycardia.

RESULTS

There were 69 men and 29 women in the final sample. At the time of ambulatory electrocardiography between 1978 and 1980, 59 subjects were in their 60s, 32 were in their 70s and 7 were aged 80 to 85 years (overall mean 69.2). The duration of electrocardiographic monitoring was 23.1 ± 2.0 hours. All 98 subjects were in normal sinus rhythm. The mean, minimal and maximum heart rates were 72 ± 9, 53 ± 7 and 112 ± 18 beats/min, respectively.

Table I delineates the prevalence of supraventricular and ventricular arrhythmias in the 98 volunteers. Isolated supraventricular ectopic beats were present in 88% and isolated VECs in 78% of subjects. Nonsustained paroxysmal supraventricular tachycardia occurred 22 times in 13 subjects and was usually <5 beats in length (range 3 to 32). Atrial fibrillation was not seen; a 2-second run of atrial flutter occurred in 1 person. Ventricular couplets were observed in 11 subjects, and a total of 5 runs of ventricular tachycardia occurred in 4 subjects (duration 3 to 13 beats). All of these supraventricular and ventricular tachyarrhythmias were asymptomatic. Transient ST-segment changes developed in 16 subjects; 5 with ≥1 mm horizontal or downsloping ST segments and 11 with ≥1 mm upsloping ST-segment depression, none of whom reported symptoms.

Over a mean follow-up of 10 years, coronary events developed in 14 subjects: angina pectoris in 7, nonfatal myocardial infarction in 3 and cardiac death in 4. The mean age of these 14 subjects, 69.9 years, and their gender distribution, 10 men and 4 women, were virtually identical to those of the overall group. The mean 24-hour heart rate (75 ± 8 vs 72 ± 9 beats/min), the maximal (116 ± 20 vs 111 ± 18 beats/min) and minimal (51 ± 6 vs 53 ± 7 beats/min) heart rates, and the mean difference between maximal and minimal heart rates (65 ± 23 vs 58 ± 19 beats/min) did not differ, respec-

TABLE II Coronary Event Rate by Arrhythmia Status

Arrhythmia	Event Rate (%) With Arrhythmia	Event Rate (%) Without Arrhythmia
Supraventricular		
≥30 supraventricular ectopic beats in any hour	18	13
≥100 supraventricular ectopic beats in 24 hours	20	12
Paroxysmal supraventricular tachycardia	15	14
Ventricular		
≥10 VECs in any hour	14	14
≥30 VECs in any hour	17	14
≥100 VECs in 24 hours	18	14
Couplets or nonsustained VT	20	13

There were no statistically significant differences between groups. Abbreviations as in Table I.

tively, between the 14 persons who experienced coronary events and the 84 who remained event-free.

In Table II, the coronary event rate for the subset with versus the subset without each arrhythmia is compared. There is no significant association between any arrhythmia category and subsequent events. Although ischemic ST-segment depression was observed in only 5 subjects, coronary events developed in 2 of them (40%) versus 12 (13%) of the 93 subjects without such ST-segment changes, p = not significant. Including the 11 additional subjects with upsloping ST-segment depression, coronary events occurred in 6 of 16 (38%) with, versus 8 of 82 (10%) without any ST-segment changes, p <0.05. Kaplan-Meier survival curves with log-rank analysis (Figure 1) demonstrated a significantly reduced event-free survival in the subset with any ST-segment changes.

If only the 7 subjects with hard events (i.e., myocardial infarction or cardiac death) are considered, there was also no association between any arrhythmia category in Table I and a subsequent event. However, 2 of the 4 subjects with short (3 to 10 beats) runs of ventricular tachycardia developed hard events (both sudden death) versus only 5 of 94 subjects without ventricular tachycardia, p <0.02. Horizontal or upsloping ST-segment depression occurred in 3 of 7 subjects (43%) with hard events versus 13 of 91 (15%) who remained event-free, p = not significant. Both subjects with nonsustained ventricular tachycardia who died suddenly also demonstrated upsloping ST-segment depression.

Although it was not considered a coronary event, sustained atrial fibrillation developed in 3 subjects over the follow-up period. Two of these 3 had paroxysmal supraventricular tachycardia during ambulatory electrocardiography compared with 12 of 95 subjects (13%) who did not develop atrial fibrillation, p = 0.08.

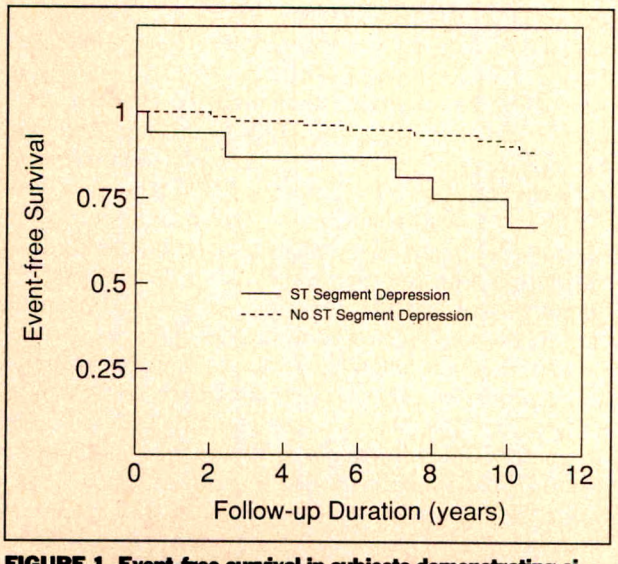


FIGURE 1. Event-free survival in subjects demonstrating either horizontal or upsloping ST-segment depression during ambulatory electrocardiography versus those without ST-segment depression. The curves differ significantly (p = 0.004 by log-rank analysis).

DISCUSSION

Several investigators during the last decade have documented an age-associated increase in cardiac arrhythmias during ambulatory monitoring in apparently normal subjects.[1-3] Because such studies were cross-sectional in design, they could not determine whether these age-related arrhythmias carried prognostic significance. In our series, neither supraventricular ectopic beats nor VECs, even if frequent, presaged an increased risk of future cardiac events. However, an association was observed between the combination of nonsustained ventricular tachycardia and ST-segment depression with subsequent sudden death. Mean, maximal and minimal heart rates were similar in the group of patients who would develop a future event and those who would not.

Prior studies addressing the prognostic significance of VECs in asymptomatic older subjects have shown conflicting results. Among 30 unmedicated asymptomatic elderly subjects, there was no correlation between the frequency of VECs on 24-hour recordings and cardiovascular symptoms nearly 2½ years later.[14] In 101 community dwelling persons aged ≥75 years, 17 of 27 with >10 VECs/hour on ambulatory monitoring died over the next 5 years versus only 27 of the 74 with fewer VECs.[7] The percentage of deaths due to cardiac causes in these 2 groups was not specified. Although Hinkle et al[15] documented an increased coronary death rate over a 2.5-year follow-up in apparently healthy middle-aged men with >10 VECs/1,000 beats, further analyses revealed that these deaths were limited to men with definite or probable coronary heart disease. Among institutionalized elderly persons without apparent heart disease, Aronow et al[8] noted similar low rates of hard coronary events over 39 ± 18 months in 34 subjects with frequent or repetitive VECs on 24-hour recordings (9%) as in 70 persons without such ectopic activity (7%); event rates for patients with nonsustained ventricular tachycardia were not reported separately. Previous studies have not examined the prognostic significance of supraventricular arrhythmias or mean 24-hour heart rates in asymptomatic older populations.

The association between nonsustained ventricular tachycardia and sudden death in this study, although anecdotal because of the very small numbers, supports

recent findings from the Multiple Risk Factor Intervention Trial.[16] These investigators found that frequent or complex VECs on a 2-minute resting ECG predicted a 4.2-fold risk of sudden cardiac death, whereas no association with nonsudden cardiac death was noted. Moreover, an association between exercise-induced ventricular arrhythmia and concomitant ST-segment changes with future cardiac events has been described.[17] In our study, some analogy may exist in the observation of 2 sudden deaths occurring in the presence of nonsustained ventricular tachycardia and upsloping ST-segment changes on the ambulatory ECG.

In general, the present data support the concept that frequent or complex VECs or supraventricular ectopic beats in persons without apparent cardiac disease carry a benign long-term prognosis. Because of the recently recognized risk of both early and late proarrhythmia associated with antiarrhythmic drug therapy,[18] such asymptomatic persons should not routinely receive these agents.

Although ischemic ST segments were uncommon, as expected in these asymptomatic volunteers with normal exercise ECGs, the subsequent development of coronary events was nearly 4 times as high in the 16 subjects with transient ST-segment shifts (including either horizontal or upsloping ST changes) as in the 82 persons without such shifts. Silent ischemia on ambulatory monitoring has been shown to predict increased coronary event rates in patients with known ischemic heart disease.[9–11] Our findings support a recent Scandinavian study which reported that ambulatory silent ischemia predicted a 4.4-fold increased risk of hard coronary events in apparently healthy 68-year-old men.[19] The present results suggest that even upsloping ST-segment shifts during ambulatory electrocardiography may have prognostic significance in asymptomatic older populations.

The present study, while generally unable to demonstrate prognostic significance for VECs or supraventricular ectopic beats in predicting future coronary events, is limited by the small number of persons who had complex arrhythmias as well as the low rate of coronary events. Both factors limit the statistical power of detecting outcome differences between groups. The coexistence of nonsustained ventricular tachycardia and ST-segment changes in 2 of the 3 subjects who died suddenly precludes determining the relative importance of these findings but suggests that the combination may be a potent indicator of increased coronary risk. Much larger studies are required to determine whether ventricular runs or ST-segment shifts are the more potent prognostic variable.

Acknowledgment: The expert secretarial assistance of Sharon Thomas and the statistical expertise of Frances O'Connor are greatly appreciated.

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Effect of High-Current Stimulation in Patients with Sustained Ventricular Tachycardia Rendered Noninducible by Antiarrhythmic Drugs

Bruce G. Hook, MD, Francis E. Marchlinski, MD, Mark E. Josephson, MD, and Alfred E. Buxton, MD

Successful antiarrhythmic drug therapy for sustained ventricular tachycardia (VT) is presumed to be related to effects on myocardium within the reentrant circuit. To test the hypothesis that prevention of VT induction may be related to effects on myocardium other than that directly involved in the tachycardia circuit, high-current stimulation was used to achieve shorter coupling intervals in 22 patients with sustained uniform VT that was rendered noninducible by antiarrhythmic agents during stimulation at twice threshold. Sustained uniform VT was induced in 10 patients in response to high-current stimulation (group 1), including 4 tachycardias with the same morphology observed in the baseline study. There were no inducible arrhythmias in 12 patients (group 2). Patients were receiving several different antiarrhythmic regimens, but there was no particular drug associated with the induction of VT using high-current stimulation. There was no statistically significant difference between groups 1 and 2 in baseline VT cycle length (247 ± 41 vs 253 ± 44 ms), drug-induced increase in effective refractory period (20 ± 15 vs 16 ± 7%), QRS duration (25 ± 10 vs 20 ± 17%) or maximal current strength delivered (10.9 ± 5.3 vs 9.3 ± 4.0 mA). There was no significant difference in local activation with high-current stimulation between groups 1 and 2. In conclusion, sustained uniform VT was induced in 45% (10 of 22) of patients whose arrhythmias were rendered noninducible by antiarrhythmic agents during programmed stimulation at twice threshold. This suggests that prolongation of refractoriness at the site of stimulation or slowing in conduction time of extrastimuli to the presumed reentrant circuit, or both, may be one mechanism by which antiarrhythmic drugs prevent induction of VT during programmed stimulation.

(Am J Cardiol 1992;70:752–757)

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The electrophysiologic properties of antiarrhythmic agents have been characterized extensively,[1,2] yet the mechanism by which they prevent induction of ventricular tachycardia (VT) remains unknown.[3,4] It is assumed that a drug's effectiveness in preventing induction of the arrhythmia is due to alterations in the electrophysiologic properties of the presumed reentrant circuit. However, because the programmed ventricular extrastimuli used to initiate VT are introduced routinely from the right ventricular endocardium, it is possible that drug-induced prolongation of refractoriness at the site of stimulation or slowing of conduction of propagating extrastimuli, or both, might limit the prematurity acheivable at the left ventricular site of origin. Thus, the drug may not alter the reentrant circuit sufficiently to prevent a tachycardia, but only influence the ability of ventricular extrastimuli to reach the circuit. The use of increased pacing current strength has been shown to decrease measured effective refractory periods in normal human[5–9] and canine[10] ventricular tissue, thereby allowing more closely coupled ventricular extrastimuli to capture during attempts at arrhythmia induction.[6,11,12] Although only limited data exist regarding the influence of antiarrhythmic agents on the strength-interval relation, studies with procainamide[13,14] have demonstrated that the curve is shifted rightward, while maintaining the same shape. The purpose of this study was to determine if the inability to induce sustained VT during drug therapy is related to alteration in local tissue properties at the site of stimulation. To test this hypothesis, we studied the ability of increased current strength to facilitate initiation of VT that was rendered noninducible by antiarrhythmic agents with programmed stimulation at twice threshold.

METHODS

Study group: The study group consisted of 22 patients (20 men and 2 women, mean age 61 ± 12 years) with sustained uniform VT inducible in the absence of drugs, and rendered noninducible by antiarrhythmic agents during programmed stimulation. Indications for electrophysiologic study were cardiac arrest in 4 patients, hemodynamically tolerated sustained uniform VT in 13, nonsustained VT in 3 and syncope in 2. Cardiac diagnoses included coronary artery disease with prior myocardial infarction in 16 patients and idiopathic dilated cardiomyopathy in 6 patients.

Baseline electrophysiologic studies: Patients initially underwent baseline electrophysiologic study in the postabsorptive state after all antiarrhythmic medications had been discontinued for at least 5 half-lives. All

patients gave informed written consent. Two to four 6Fr quadripolar electrode catheters (USCI, 5 mm interelectrode distance) were inserted percutaneously into the femoral veins and advanced to the heart under fluoroscopic guidance. Programmed stimulation was performed with a custom-designed programmable stimulator and an optically isolated constant current source (Bloom Associates Ltd.; Reading, Pennsylvania) that delivered rectangular pulses 1 ms in duration at twice diastolic threshold. Bipolar electrograms were filtered at 40 to 400 Hz and displayed simultaneously with ≥3 surface electrocardiographic leads (usually 1, 2 or a VF and V_1) on a multichannel oscilloscope (Electronics for Medicine, VR 16). Data were recorded simultaneously with an ink jet recorder (Siemens Mingograf, 100 or 200 mm/s paper speed) and magnetic tape (Honeywell model 5600). The stimulation protocol, which has been described previously,[15] included pacing from the right ventricular apex and outflow tract at 2 drive cycle lengths (usually 600 and 400 ms) with the introduction of 1, 2 or 3 ventricular extrastimuli and rapid ventricular pacing. Sustained uniform VT was induced in all patients in the baseline study. A tachycardia was designated as sustained if it lasted >30 seconds or required cardioversion before 30 seconds because of severe hemodynamic compromise.

Serial drug testing: After the baseline study, patients underwent serial drug testing until an antiarrhythmic regimen was found that successfully prevented induction of the tachycardia during stimulation at twice threshold. Noninducibility during stimulation at twice threshold and at high-current strength was defined by the absence of inducible sustained ventricular arrhythmias with delivery of 3 ventricular extrastimuli from 2 right ventricular sites at 2 drive cycle lengths.

Stimulation protocol at the higher current strength: The aim of pacing at a higher current strength was to achieve ventricular capture of all extrastimuli at the same stimulus coupling intervals that induced VT in the baseline study. After completing the standard stimulation protocol, the pacing current strength was increased by 2 to 5 mA and programmed stimulation was repeated. If ventricular capture could not be achieved at the coupling intervals that induced the arrhythmia in the baseline study, the current was increased by the same amount and stimulation was repeated. This was performed initially at the same site and at the same drive cycle length used for arrhythmia induction during the baseline study. If capture was achieved at the same intervals used for arrhythmia induction at baseline without initiating a sustained ventricular arrhythmia, stimulation was performed from the second right ventricular site. The end point of the stimulation protocol using the high-current strength was induction of sustained uniform VT or ventricular capture of all extrastimuli at the same stimulus coupling intervals that induced VT in the baseline study.

Comparison of patients with and without inducible sustained ventricular tachycardia using high-current stimulation: Based on the response to stimulation at the high-current strength, patients were classified into 2 groups: Group 1 consisted of patients with inducible sustained VT, whereas group 2 included patients whose arrhythmias remained noninducible. To determine if any differences between the 2 groups were associated with the induction of a sustained ventricular arrhythmia during high-current stimulation, we compared antiarrhythmic drug regimens as well as drug-induced changes in local refractory periods, ventricular activation time, minimal coupling intervals achieved and maximal current strength delivered. In addition, to determine whether the induction of VT using higher current stimulation in group 1 was dependent on achieving the same coupling intervals that initiated the tachycardia in the baseline study, we compared in each patient the coupling intervals of the extrastimuli associated with tachycardia induction at the 2 study periods.

Measurement of local activation time: Whereas pacing with increased current strength permits ventricular capture at shorter stimulated intervals, prolonged local latency may preclude reduction in the corresponding local and distant activation times.[7,8] As such, coupling intervals were measured from the ventricular electrogram recorded from the proximal electrode pair of the pacing catheter positioned at either the right ventricular apex or outflow tract. These intervals were designated as V_1–V_2, V_2–V_3 and V_3–V_4. Since left ventricular catheters were not in place during stimulation, measurement of coupling intervals achieved at the left ventricular site of origin, which would reflect any conduction delay in the intervening tissue, could not be performed.

Management: All drug regimens were considered to have been successful for purposes of clinical management, since arrhythmia induction was prevented using the standard stimulation protocol at twice diastolic threshold. However, only 12 of 24 patients were discharged on the drug regimen present during the study protocol, either because of adverse effects of the drug (n = 6) or the intravenous administration of the study drug (n = 6). Because follow-up was confounded by the presence of therapies other than those studied during the experimental protocol, the incidence of VT recurrence in groups 1 and 2 could not be assessed.

Statistics: Comparisons within groups before and after drug therapy were performed using a paired *t* test, whereas analysis of differences between patients with and without inducible VT at the higher current strength was performed with an unpaired *t* test. Differences were considered significant at $p < 0.05$.

RESULTS

Induction of sustained uniform ventricular tachycardia with higher current strength stimulation: Sustained uniform VT was induced in 10 patients (group 1) in response to programmed stimulation at the higher current strength. The mean cycle length of these tachycardias was 309 ± 53 ms. No arrhythmias were inducible in 12 patients (group 2). There was no significant difference (p = not significant) between groups 1 and 2 in the mean baseline VT cycle length (247 ± 41 vs 253 ± 44 ms), maximal current strength delivered (10.9 ± 5.3 vs 9.3 ± 4.0 mA) or drug-induced increases in refractoriness or conduction time (Table I). An example of the induction of sustained uniform VT at the higher

TABLE I Effects of Antiarrhythmic Drug Therapy on Effective Refractory Period (ERP) and QRS Duration

	Group 1	Group 2
ERP*		
Baseline (ms)	233 ± 25†	235 ± 29
Drugs (ms)	278 ± 30	271 ± 30
% change	20 ± 15	16 ± 7
QRS*		
Baseline (ms)	161 ± 18	159 ± 30
Drug (ms)	201 ± 23	189 ± 31
% change	25 ± 10	20 ± 17

*Recorded during stimulation from the right ventricular apex at a drive cycle length of 400 ms.
†p = not significant for all comparisons between groups 1 and 2.

current strength is shown in Figure 1. Four of the 10 tachycardias induced at the higher current strength demonstrated the same morphology (12 lead electrocardiogram) as in the baseline study (Figure 2), suggesting that the original tachycardia circuit remained despite the absence of inducible arrhythmias at twice threshold. In the presence of antiarrhythmic agents, the mean cycle length of these 4 tachycardias increased from 220 ± 18 to 309 ± 50 ms ($p < 0.005$).

Effects of high-current stimulation on the mode of ventricular tachycardia induction during drug therapy in group 1: Whereas the use of higher pacing current strength during drug therapy allowed shorter coupling intervals to be achieved relative to those at twice threshold, we sought to determine whether the mode of VT induction was affected by the presence of antiarrhythmic agents. VT was initiated from the same site in both studies in 8 of 10 patients, with the same drive cycle length in 7 of 10 patients and with the same number of ventricular extrastimuli in 8 of 10 patients (Table II). Compared with the baseline study, coupling intervals initiating VT at the higher current strength were longer in 9 of 10 patients. The mean coupling intervals initiating VT at the higher current strength were significantly longer than during the baseline study (Table III).

Coupling intervals achieved at the higher current strength: To determine whether the induction of VT in group 1 was due to achieving shorter coupling intervals relative to group 2, the coupling intervals initiating VT in these patients were compared with the shortest coupling intervals achieved in group 2 (Table IV). There were no significant differences between groups 1 and 2 in the shortest V_1–V_2, V_2–V_3 and V_3–V_4 interval. In all patients in group 2, stimulus coupling intervals achieved were equal to or shorter than those initiating VT in the baseline study. Thus, the induction of VT in group 1 could not be explained by the shorter coupling intervals of local activation when compared with group 2.

DISCUSSION

This study demonstrates that programmed stimulation using up to 3 extrastimuli introduced at a higher current strength can initiate sustained uniform VT in 45% (10 of 22) of patients whose arrhythmia was ren-

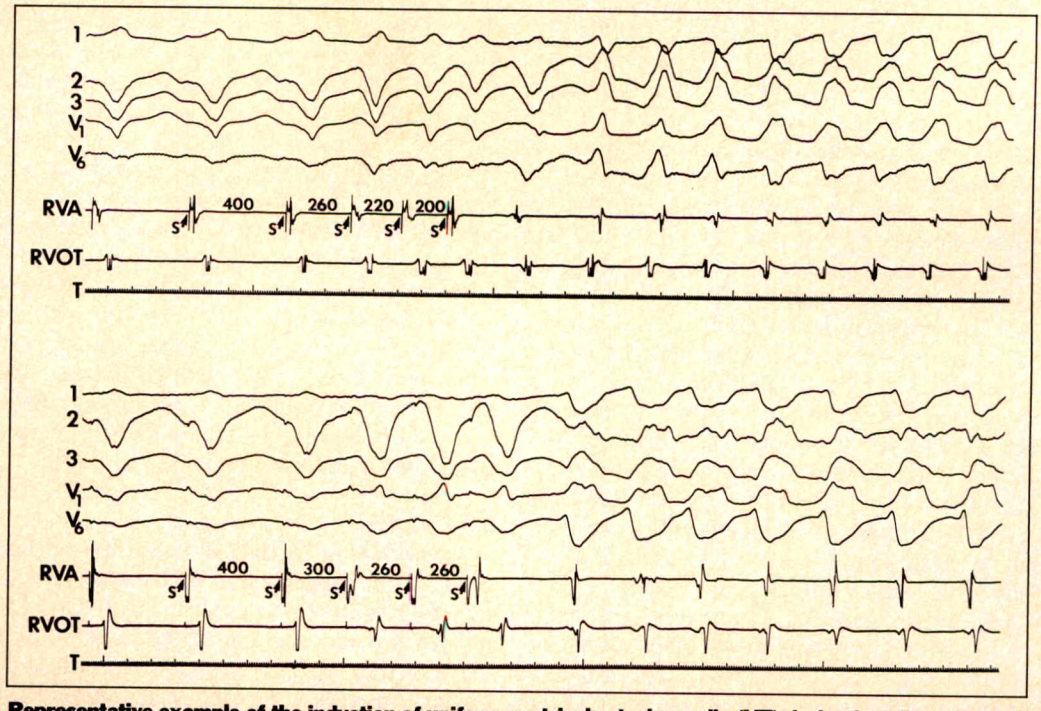


FIGURE 1. Representative example of the induction of uniform ventricular tachycardia (VT) during baseline study and with high-current stimulation in the presence of quinidine and mexiletine. Surface leads 1, 2, 3, V_1 and V_6 are shown along with intracardiac recordings from the right ventricular apex (RVA) and right ventricular outflow tract (RVOT) in both *panels*. *Top*, triple extrastimuli delivered from the RVA initiate uniform VT with a cycle length of 230 ms. The morphology demonstrates a right bundle branch block pattern in lead V_1 and the axis is directed rightward and inferiorly. *Bottom*, with stimulation at 10 mA, triple extrastimuli again initiate uniform VT. The morphology and axis are similar to the tachycardia induced during the baseline study. Whereas high-current stimulation permitted shorter coupling intervals to be achieved during drug therapy, they were nonetheless greater than those that initiated the arrhythmia during the baseline study. In the presence of quinidine and mexiletine, the tachycardia cycle length increased to 390 ms.

TABLE II Effects of Antiarrhythmic Drug Therapy and High-Current Stimulation on Mode of Ventricular Tachycardia Induction in Group 1

	Baseline*			Drug + High Current			
Pt. No.	Site	Drive CL (ms)	Coupling Intervals (V_2 /V_3 /V_4)	Site	Drive CL (ms)	Coupling Intervals (V_2 /V_3 / V_4)	Current Strength (mA)
1	RVA	400	260/230/200	RVOT	600	300/240/240	5
2	RVOT	600	260/200/180	RVOT	400	290/290/270	10
3	RVOT	400	240/190/180	RVOT	400	290/270/240	20
4	RVOT	400	260/220/210	RVOT	400	310/290/290	10
5	RVA	400	250/220/—	RVA	400	250/220/—	4
6	RVA	400	240/190/190	RVA	400	310/270/240	10
7	RVA	400	240/190/—	RVA	400	260/240/210	10
8	RVA	400	270/210/190	RVA	400	290/260/260	10
9	RVOT	600	240/190/180	RVA	400	265/265/—	20
10	RVOT	400	285/220/195	RVOT	400	240/240/230	10

*Pacing threshold <1 mA in all patients; stimulus strength <2 mA in all patients.
CL = cycle length; RVA = right ventricular apex; RVOT = right ventricular outflow tract.

dered noninducible by antiarrhythmic agents during stimulation at twice diastolic threshold. The induction of sustained VT in these patients was unrelated to differences in antiarrhythmic drug regimen, baseline tachycardia cycle length, indexes of drug effects on refractoriness and conduction velocity, maximal pacing current strength delivered, or local coupling intervals achieved at the higher current strength when compared with values in patients whose arrhythmias remained noninducible.

Role of increased current strength in initiating sustained ventricular tachycardia: In the absence of antiarrhythmic agents, the use of current strengths up to 20 mA has been shown to reduce the measured ventricular effective refractory period by approximately 34 to 45 ms.[5–8,13] Similarly, during therapy with procainamide, the effective refractory period has been found to decrease by about 25 to 40 ms because the stimulus intensity is increased from twice threshold to 20 mA.[13,14] Because arrhythmia induction is usually facilitated by shortening extrastimuli coupling intervals, this would appear to be one mechanism by which increased current strength could promote arrhythmia induction. However,

TABLE III Mean Coupling Intervals Inducing Ventricular Tachycardia in Group 1 at Baseline Compared with Higher Current Strength During Drug Therapy

	V_1–V_2	V_2–V_3	V_3–V_4
Baseline (ms)	253 ± 12	206 ± 16	191 ± 11
Drug (ms)	275 ± 26*	256 ± 22†	246 ± 26†

*$p<0.05$ baseline versus drug; †$p<0.005$ baseline versus drug.

although Kennedy et al[12] noted that the coupling intervals initiating ventricular fibrillation at high-current strength in the absence of antiarrhythmic agents were shorter than those achievable at twice threshold in all patients, Morady et al[11] found that in 4 of 16 patients with inducible arrhythmias only at 10 mA the coupling intervals were equal to or longer than the shortest coupling intervals resulting in ventricular capture at twice threshold. Similarly, Hamer et al[16] found reproducible induction of ventricular fibrillation at high-current strengths but not at lower currents at almost identical coupling intervals in 4 of 22 episodes of ventricular

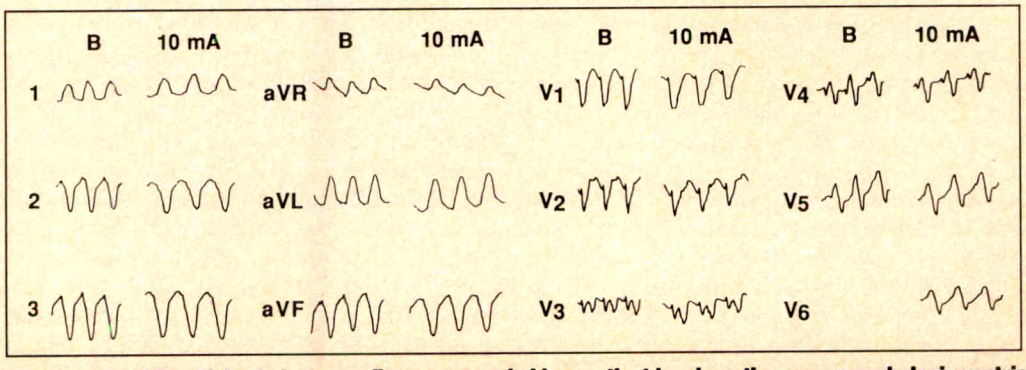


FIGURE 2. An example of the 12-lead electrocardiogram recorded in a patient in whom the same morphologic ventricular tachycardia was induced in the baseline state and with higher current stimulation during procainamide therapy. There were no inducible arrhythmias at twice threshold in the presence of procainamide. For each *column*, the tracings on the *left (B)* are from the baseline study, whereas those on the *right* (10 mA) were recorded during treatment with procainamide. Note that in every lead recorded the QRS morphology is nearly identical in the 2 tracings. This suggests that the original ventricular tachycardia circuit was still present despite no inducible arrhythmias during stimulation at twice threshold. The tachycardia cycle length increased in the presence of the drug from 240 to 290 ms.

TABLE IV Minimal Coupling Intervals Achieved Using High-Current Stimulation

	V_1–V_2	V_2–V_3	V_3–V_4
Group 1 (ms)*	275 ± 26	256 ± 22	246 ± 26
Group 2 (ms)	270 ± 36†	245 ± 33†	243 ± 38†

*Coupling intervals (ms) are those that induced ventricular tachycardia.
†p = not significant, group 1 versus group 2.

fibrillation in 8 normal dogs. These data have suggested that factors in addition to producing local capture at shorter coupling intervals may contribute to the influence of increased current strength on ventricular tachyarrhythmia induction. Indeed, Meesman and Marchlinski[17] reported the presence of changes in the pattern and timing of local and distant activation with increases in current strength. A recent study[18] has also demonstrated that the shortening of an effective refractory period achieved with high-current stimulation may be attenuated by autonomic blockade, suggesting that enhanced catecholamine release may be partially responsible for the observed effects of high-current stimulation. In the present study, initiation of VT at the higher current strength was associated with local activation at shorter coupling intervals than those achieved at twice threshold, suggesting this as the mechanism for facilitation of arrhythmia induction.

Morphology of ventricular tachycardia induced with higher current strength compared with baseline: Four of the 10 tachycardias induced during drug therapy only with higher current stimulation demonstrated the same morphology as in the baseline study, implying that the original tachycardia circuit persisted. The other 6 tachycardias had not been observed previously. However, this does not necessarily indicate that the induction of these arrhythmias represented a "nonspecific" response. These tachycardias were all of uniform morphology, as opposed to the more nonspecific polymorphic VT that has been noted with stimulation at increased current strength.[5,11,12] Furthermore, the induction of previously undocumented morphologies of uniform VT only in the presence of antiarrhythmic agents is not uncommon.[19,20] Because it is rare to have 12-lead electrocardiographic documentation of all spontaneously occurring morphologies of VT in a given patient, the induction of a uniform tachycardia only after drug therapy may represent the manifestation of a fixed reentrant pathway that was not expressed during the baseline study.

Coupling intervals initiating ventricular tachycardia at increased current strength compared with twice threshold: In 9 of 10 patients in group 1 the coupling intervals initiating VT during stimulation with increased current strength were greater than those that induced the arrhythmia in the baseline study (Table III). These results are similar to those obtained with pacing at twice threshold[21,22] in patients whose arrhythmias remained inducible in the presence of antiarrhythmic agents. This suggests that drug-induced prolongation of refractoriness or slowing of conduction velocity, or both, may facilitate the unidirectional block required to initiate reentry, so that VT can be initiated with extrastimuli introduced at longer coupling intervals. In using this argument, the inability to induce arrhythmia at twice threshold would have been due to failure of the extrastimuli to reach the tachycardia circuit with sufficient prematurity.

Role of increased refractoriness at the site of stimulation in preventing induction of ventricular tachycardia: Because of the difficulty in recording directly from tissue within the reentrant circuit, efforts to understand the actions of antiarrhythmic agents in preventing induction of VT have often involved attempts at correlating measured changes in global conduction and refractoriness with the ability to induce the arrhythmia.[3] Implicit in this approach is that (1) the effects on myocardium within the reentrant circuit are similar to those that were recorded, and (2) the prevention of VT induction is related to effects on myocardium within the tachycardia circuit. However, procainamide has been found to increase both conduction time[23] and refractoriness[14] to a greater extent in infarcted myocardium than in normal tissue. The data from the present study suggest that drug effects on tachycardia induction may be unrelated to the reentrant circuit (i.e., antiarrhythmic agents may act on normal tissue to prevent extrastimuli from arriving at the tachycardia circuit with sufficient prematurity to produce unidirectional block and reentry). Thus, it is not surprising that clinical studies have failed to demonstrate conclusively a relation between the increase in refractoriness at the site of stimulation and the ability to prevent induction of the arrhythmia.[24–30]

Study limitations: Several limitations in this study are worth noting: (1) Coupling intervals were not measured at the left ventricular site of origin, and thus the prematurity of the extrastimuli achieved at the tachycardia circuit can only be inferred. (2) The influence of antiarrhythmic therapy on myocardial tissue within the presumed reentrant circuit was not assessed. Obviously, this was not possible in group 2 because arrhythmias were not inducible either at twice threshold strength or with higher current stimulation. (3) Initiation of an arrhythmia with the higher current strength may have been due to the effects of repetitive stimulation.

Clinical implications: We have demonstrated that programmed stimulation at a higher current strength can induce sustained uniform VT in 45% of patients whose arrhythmias are noninducible at twice threshold during antiarrhythmic drug therapy. It is tempting to speculate that patients with inducible arrhythmias at the higher current strength may be at greater risk for arrhythmia recurrence due to persistence of the tachycardia circuit. However, this study was not designed to answer this question, and one cannot conclude from these data that the induction of VT using high-current stimulation during drug therapy implies a higher risk of recurrent arrhythmia. Rather, these data suggest that prevention of arrhythmia induction may be related to effects other than those on the presumed reentrant circuit.

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Reproducibility of Programmed Electrical Stimulation Responses in Patients with Ventricular Tachycardia or Fibrillation Associated with Coronary Artery Disease

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Invasive electrophysiologic studies were performed in 102 patients with sustained ventricular tachycardia (VT) or ventricular fibrillation (VF) using an aggressive programmed electrical stimulation (PES) protocol. The study was repeated after 2.0 ± 2.9 days in all patients with no intercurrent changes in antiarrhythmic therapy. Patients with coronary artery disease (n = 72) were identified and PES results of these patients were analyzed and compared with results of patients without coronary artery disease. Multiple clinical and electrophysiologic factors were analyzed to determine any association with concordance of PES responses. No significant difference in concordance of PES responses was found in the 2 groups of patients. PES responses were grouped into 3 categories: (1) noninducible, (2) nonsustained VT, and (3) sustained VT. Kappa values of PES responses of noninducible and sustained VT in both groups were higher and therefore the PES responses were more reproducible than nonsustained VT. The induction of sustained monomorphic VT was more reproducible than a PES response of nonsustained or sustained polymorphic VT. Inducible sustained VT with a rate of ≥250 beats/min was less reproducible than induction of sustained VT with a rate <250 beats/min. Induction of VT by 3 extrastimuli was less reproducible than with any other mode. This short-term variability may account for false negatives associated with PES-directed antiarrhythmic therapy. Because of these findings, it is recommended that nonsustained VT and sustained polymorphic or rapid polymorphic VT should not be used as PES end points to guide antiarrhythmic therapy.

(Am J Cardiol 1992;70:758–763)

The use of programmed electrical stimulation studies (PES) has become widely accepted as a clinical tool in the management of patients with sustained ventricular tachycardia (VT) or ventricular fibrillation (VF). PES studies have been suggested to be better than the noninvasive approach in assessing risk and directing antiarrhythmic therapy in these patients.[1] The Electrophysiologic Study Versus Electrocardiographic Monitoring trial, a multicenter, randomized trial is underway to help elucidate this issue.[2] With the advent of more effective antiarrhythmic therapy, including drugs and devices, it is even more crucial to understand the sensitivity, specificity, predictive accuracy and reproducibility of PES studies. PES studies have been shown to have >90% sensitivity in patients with recurrent sustained VT and >90% specificity in patients without clinical VT.[3] When PES studies are used to predict suppression of arrhythmic recurrence with antiarrhythmic drugs, it has 85 to 100% accuracy.[4–7] The sensitivity of PES is affected by clinical factors and presenting arrhythmia. Factors that influence the reproducibility of PES are still unclear. The immediate reproducibility of sustained VT induction has been found to be high (77 to 98%),[8,9] whereas late reproducibility (i.e., weeks to months) was found to be variable in canine infarct models[10] and in patients with previous infarctions.[11–13] Since decisions regarding antiarrhythmic therapy for high-risk patients need to be made in a timely fashion, the therapy is usually based on 1 PES study. It is important to determine its reproducibility from day to day as well as its immediate reproducibility. Day-to-day reproducibility of PES response has a wider range (57 to 97%) than that of immediate reproducibility.[3,14–18] These findings may in part be due to the lack of uniformity in the definitions of the induced ventricular tachyarrhythmias as well as differences in the protocols used. These previous studies did not evaluate the factors that may influence concordance of PES responses. This study was undertaken to determine factors that may account for day-to-day variability and to identify subgroups that have more reproducible PES responses.

METHODS

Between June 1987 and September 1989, 110 consecutive patients with documented sustained VT or VF were evaluated. Patients with VT or VF related to acute infarction, electrolyte disturbance or drug intoxication were excluded. A total of 102 patients consented to ad-

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ditional PES studies to determine its reproducibility, and 25 of these patients underwent additional reproducibility studies while taking antiarrhythmic therapy resulting in a total of 127 PES studies. Seventy-two patients were identified as having coronary artery disease by coronary arteriogram. The studies were performed in the drug-free control state in 84 patients or while receiving predischarge antiarrhythmic therapy in 43 patients. No changes were made in antiarrhythmic therapy in the 2 studies. All patients underwent PES studies on 2 separate days. Patients treated with an antiarrhythmic agent underwent their first PES study (PES-1) after achieving a steady-state level (treatment for at least 4 half-lives of the medication). Patients treated with amiodarone (n = 14) had PES-1 performed after 7 to 10 days of amiodarone therapy with a dose of 1,200 mg/day. No intravenous drug testing was performed in any of the patients. A drug washout period of ≥5 serum elimination half-lives was allowed before performance of PES-1. No patients previously taking amiodarone were included. The second PES study (PES-2) was performed 2.0 ± 2.9 days after PES-1.

Study population: Table I summarizes the characteristics of the study population.

Programmed electrical stimulation protocol: PES was performed in the postabsorptive state. Standard quadripolar electrode catheters were inserted percutaneously into femoral veins. Catheters were positioned at the right ventricular apex and outflow tract. Intracardiac recordings were displayed simultaneously with surface electrocardiographic leads I, aVF, V_1 and V_6 on a multichannel oscilloscope recorder (Gould Electronics) and recorded at paper speeds of 50 or 100 mm/s. Cardiac stimulation was performed using a programmable stimulator (Bloom Associates, Ltd.) delivering rectangular pulses with stimulation duration of 2 ms and twice the mid-diastolic threshold for current strength. The pacing catheters were removed at the conclusion of each study. A new pacing catheter was inserted for each subsequent study.

PES was performed with single and double extrastimuli using 8-beat drive trains at 3 drive cycle lengths of 600, 500 and 400 ms. The premature stimulus was initially positioned 300 ms after the last stimulus. Effective refractory periods of the extrastimulus were achieved with decrements of 10 ms. Burst pacing of 4 to 8 consecutive beats was delivered from 300 to 240 ms or until 2:1 capture was achieved. The stimulation protocol was first done at the right ventricular apex then at the right ventricular outflow tract. Triple extrastimuli were introduced at the same 3 drive cycle lengths. The study was terminated with the induction of a sustained ventricular tachyarrhythmia that required cardioversion, or with completion of the protocol. If a monomorphic VT was induced, hemodynamic compromise was assessed by blood pressure monitoring and consciousness. If the VT persisted after 30 seconds, overdrive pacing was attempted. If the patient was stable, efforts were made to reproduce the VT or induce other VTs.

The characteristics of PES responses compared were: (1) inducibility, (2) sustainability, (3) morphology (monomorphic vs polymorphic), (4) mode of induction, and (5) cycle length of the VT. Functional refractory periods were measured and compared for reproducibility.

TABLE I Characteristics of Study Population

Patient population (n = 102)	
Age (mean ± SD years)	60 ± 14
Men/women	79/23
Organic heart disease	
Coronary artery disease	72
RV dysplasia	1
Idiopathic dilated cardiomyopathy	11
Mitral valve prolapse	5
Other valvular disease	6
Long QT syndrome	2
Tetralogy of Fallot	1
No detectable heart disease	4
LVEF (mean ± SD, n = 102)	37% ± 14%
Presenting arrhythmia	
Sustained ventricular tachycardia (n = 61)	
Ventricular fibrillation (n = 41)	
No. of days between studies (mean ± SD)	2.0 ± 2.9
Distribution of PES studies	
Control drug-free state (n = 84)	
Predischarge antiarrhythmic therapy (n = 43)	
Total number of PES comparisons (n = 127)	
Treatment	
Surgical ablation (n = 7)	
Amiodarone (n = 14)	
Sotalol (n = 20)	
Verapamil (n = 1)	
Procainamide (n = 1)	

LVEF = left ventricular ejection fraction; PES = programmed electrical stimulation; RV = right ventricular.

Definitions: PROGRAMMED ELECTRICAL STIMULATION RESPONSE CATEGORIES: (1) noninducible = <7 ventricular beats; (2) nonsustained VT = ≥7 ventricular beats but <30 seconds; (3) sustained VT = ≥30 seconds in duration or required termination because of hemodynamic compromise.

INDUCIBLE VENTRICULAR TACHYCARDIA: Either nonsustained or sustained VT (note: When ≥1 VT was induced, the longest one was reported as the PES response).

MONOMORPHIC VENTRICULAR TACHYCARDIA: Identical beat-to-beat QRS morphology in all recorded surface leads.

POLYMORPHIC VENTRICULAR TACHYCARDIA: ≥2 different QRS morphologies in surface leads.

FUNCTIONAL REFRACTORY PERIOD: The shortest achievable coupling interval for (1) V_1V_2 for 1 extrastimulus; (2) V_2V_3 for 2 extrastimuli; and (3) V_3V_4 for 3 extrastimuli.

Statistics: Continuous data are expressed as mean ± SD. Comparisons of differences between groups were evaluated using the 2 sample *t* test for continuous variables and chi-square or Fisher's exact test for discrete variables. A p value <0.05 was considered statistically significant. The kappa statistic[19] (a measure of reproducibility) and its 95% confidence interval were calculated for each category. A kappa value <0.40 indicates

poor to fair reproducibility and 0.41 to 0.60 indicates moderate reproducibility. Kappa values >0.80 indicate excellent reproducibility.[20]

RESULTS

Patient population: The 102 patients were divided into 2 groups according to presence of coronary artery disease. Results of PES responses of the 72 patients with and the 30 patients without coronary artery disease were studied in detail and compared. No significant difference in concordance of PES responses was found in the 2 groups of patients.

Programmed electrical stimulation response characterization: PES responses were grouped into 3 categories: (1) noninducible, (2) nonsustained VT, and (3) sustained VT. Results are listed in Figure 1. Response categories of noninducible or sustained VT were more reproducible (kappa >0.40) than the response category of nonsustained VT. Thus, a response of nonsustained VT is more likely to occur randomly in both patient groups. This wide 95% confidence interval reflects a lack of reproducibility for this end point.

Features of induced ventricular tachycardia: Analysis of the morphology and sustainability of induced VT is depicted in Figure 2. The induction of sustained monomorphic VT was the most reproducible VT, and nonsustained monomorphic VT was the second most reproducible response. Polymorphic VT, either sustained or nonsustained, was less reproducible in both patient groups.

Rate of induced ventricular tachycardia: Figure 3 shows that in both patient groups, slow (<250 beats/min) sustained VT was more reproducible than fast (≥250 beats/min) sustained VT. Induction of slow nonsustained VT was also more reproducible than induction of fast nonsustained VT. Figure 4 shows that slow monomorphic VT was more reproducible than fast monomorphic VT, and both slow and fast polymorphic VT.

Mode of induction: Sustained, monomorphic and slow VTs induced by a mode other than 3 extrastimuli were more reproducible than the other responses, with kappa values >0.40. Monomorphic VT induced by any mode other than 3 extrastimuli was the largest and most reproducible subset: kappa 0.47 in patients with and kappa 0.52 in patients without coronary artery disease.

Functional refractory periods: Mean functional refractory period differences were analyzed in both right ventricular sites, all stimulation modes and all drive cy-

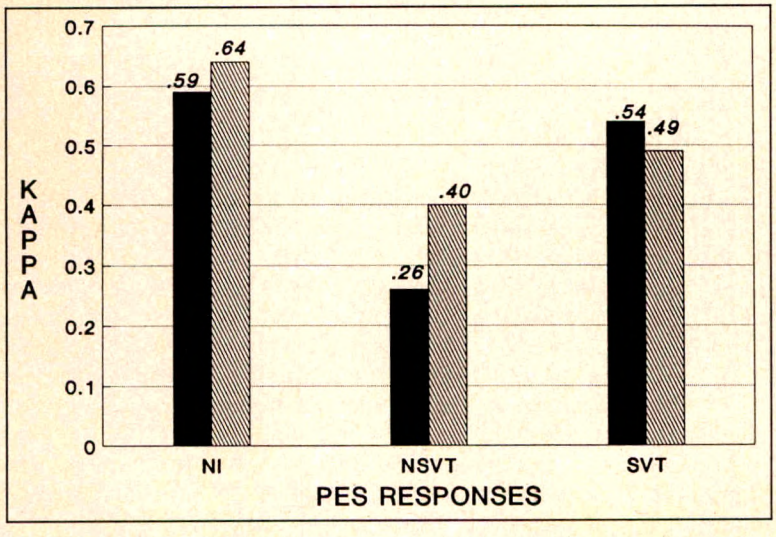


FIGURE 1. Reproducibility of programmed electrical stimulation (PES) response categories. *Solid bar graphs* represent kappa values for patients with coronary artery disease; *slashed bar graphs* represent kappa values for patients without coronary artery disease. NI = noninducible; NSVT = nonsustained ventricular tachycardia; SVT = sustained ventricular tachycardia.

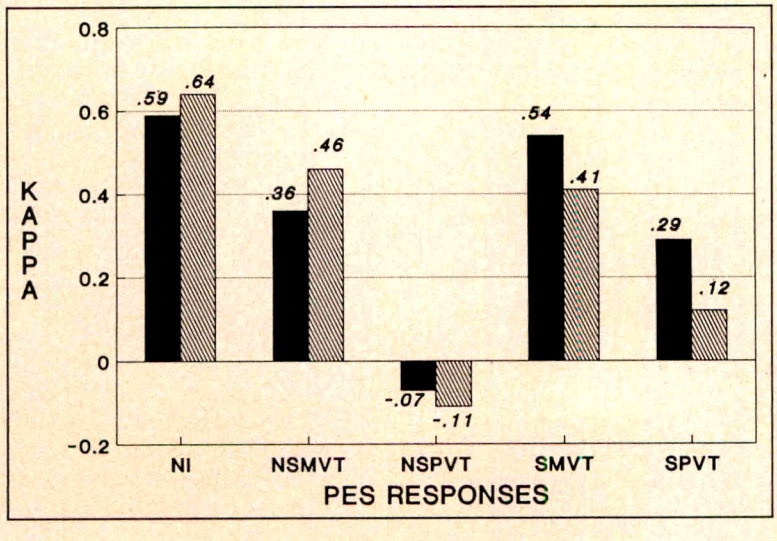


FIGURE 2. Reproducibility of features of induced ventricular tachycardia (VT). *Solid bar graphs* represent kappa values for patients with coronary artery disease; *slashed bar graphs* represent kappa values for patients without coronary artery disease. NI = noninducible; NSMVT = nonsustained monomorphic VT; NSPVT = nonsustained polymorphic VT; PES = programmed electrical stimulation; SMVT = slow monomorphic VT; SPVT = sustained polymorphic VT.

cle lengths. Comparisons were made between patients in whom PES responses were discordant versus those with concordant PES responses. There was no difference in the mean functional refractory periods between the 2 groups.

Clinical factors: No clinical factor influenced the reproducibility of PES responses. Specifically age, left ventricular ejection fraction, presenting arrhythmia or antiarrhythmic therapy were found not to affect concordance of PES responses.

DISCUSSION

There have been previous studies on day-to-day variability of PES responses; however, it remains unclear which subgroup of patients and which factors significantly influence PES reproducibility. This study is the first to suggest that PES in patients without coronary artery disease have similar reproducibility as that in patients with coronary artery disease. This needs to be validated by a study using a larger population. Unlike previous studies on reproducibility, our study analyzed the end points obtained by using 3 extrastimuli, a more aggressive stimulation protocol in patients with coronary artery disease. Our stimulation protocol is currently more widely used than those used in previous studies on reproducibility. This study also analyzed in detail the different PES responses.

This study found 2 response subgroups that had good reproducibility based on the end point of the study: patients who were noninducible and patients whose response was sustained monomorphic VT. The response of nonsustained VT was less reproducible. Using nonsustained VT as a PES end point, Podrid et al[21] showed a low recurrence rate after an average follow-up of 21 months in patients with VT or VF and syncope. However, we believe that in patients with a history of sustained ventricular tachyarrhythmia, 2 PES studies may be necessary to confirm lack of inducibility of a sustained ventricular tachyarrhythmia.

We concur with other investigators[14,15,17,22] who recommended that 2 PES studies should be performed in certain groups of patients because of day-to-day variability in PES response in the drug-free state and in the steady state of an antiarrhythmic drug. It has been shown that patients in whom inducible sustained VT cannot be suppressed by antiarrhythmic drugs are at considerable risk for arrhythmic recurrence.[7] Since effective alternate forms of therapy (e.g., implanted devices) are available in this patient population, it becomes essential to confirm that inducible VT has been

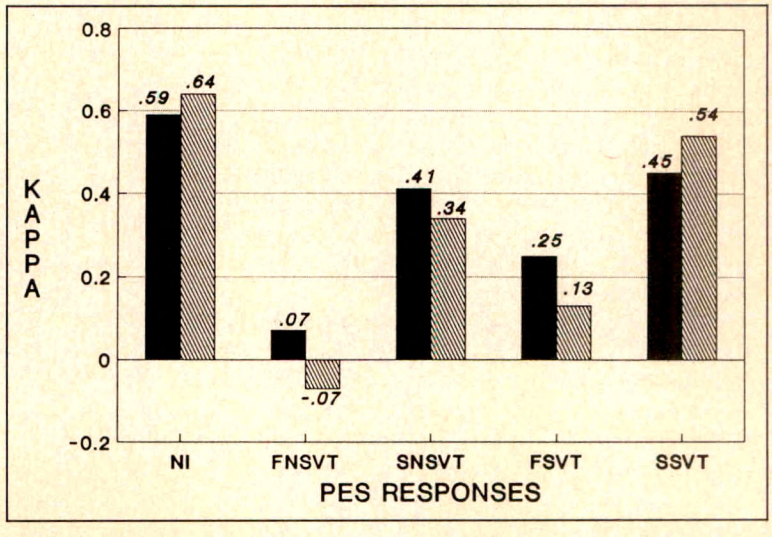


FIGURE 3. Reproducibility by rate and duration of induced ventricular tachycardia (VT). Slow is <250 beats/min; fast is ≥250 beats/min. *Solid bar graphs* represent kappa values for patients with coronary artery disease; *slashed bar graphs* represent kappa values for patients without coronary artery disease. FNSVT = fast nonsustained VT; FSVT = fast sustained VT; SNSVT = slow nonsustained VT; SSVT = slow sustained VT. Other abbreviations as in Figures 1 and 2.

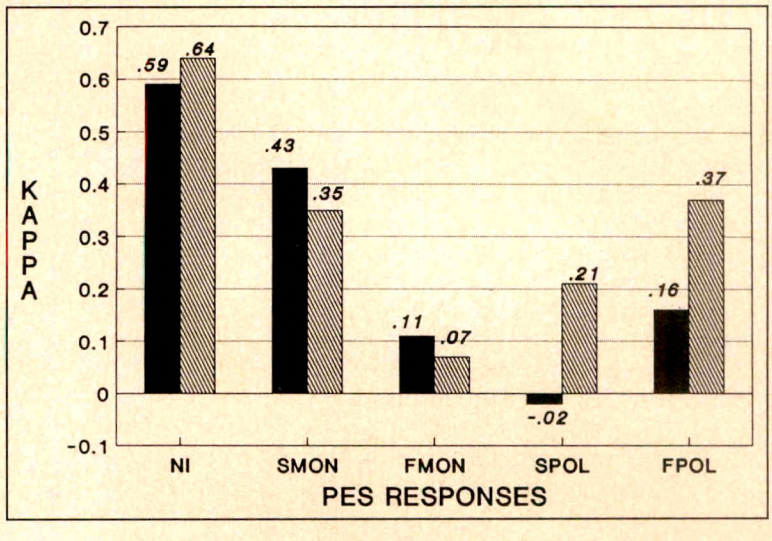


FIGURE 4. Reproducibility of the rate and morphology of the programmed electrical stimulation (PES) response. *Solid bar graphs* represent kappa values for patients with coronary artery disease; *slashed bar graphs* represent kappa values for patients without coronary artery disease. FMON = fast monomorphic ventricular tachycardia (VT); FPOL = fast polymorphic VT; NI = noninducible; SMON = slow monomorphic VT; SPOL = slow polymorphic VT.

effectively suppressed. However, because of the rising costs of medical care, repeating PES studies to confirm results is not cost-effective. It is more reasonable to select patients who should have PES responses confirmed, such as patients with responses of nonsustained or polymorphic VT. Because a response of polymorphic VT is known to be more nonspecific and not reproducible, it should not be used as an end point to guide therapy.

It has been shown that increasing the number of extrastimuli increases the sensitivity of PES.[16,23–25] However, specificity and reproducibility of PES may decrease with more extrastimuli.[14,17] This study shows that induction with 3 extrastimuli produces a less reliable PES response than the other modes used (kappa values all <0.40).

No significant day-to-day variability was found in functional refractory periods to explain the variability of PES responses. No clinical factors were found that could identify subgroups of patients who may have a more reproducible PES response. The type of presenting arrhythmia and extent of left ventricular dysfunction were notable among the clinical factors examined in our study.

Other factors that cannot be easily controlled may contribute to the variability of PES responses. These include: (1) changes in autonomic tone,[26–29] (2) duration of catheter placement,[30] and (3) day-to-day changes in local myocardial conditions.[31–33] These changes are probably not present when immediate reproducibility is assessed and may account for the higher reproducibility. It is unclear whether varying the strength and duration of stimulation pulses would increase the reproducibility without compromising the sensitivity and specificity of PES. Since some studies use 3 times the mid-diastolic threshold for cardiac stimulation, a study to control for this factor may be helpful.

Ventricular functional refractory periods and pacing thresholds increase when a catheter is left in place after 24 hours. This is obviated by daily catheter placement.[30] In our study, a new pacing catheter was placed for each study. Changes in the local myocardial conditions that may occur from day to day are difficult to investigate; some of these changes include pH, hypoxia, ischemia, and cellular electrolyte levels.[31–33] Whatever factors are responsible for this variability could also be clinically important and lead to arrhythmia recurrences even in patients rendered noninducible by antiarrhythmic therapy.

Study limitations: Because there is no standard PES protocol for evaluating VT, the reproducibility rates obtained may be protocol dependent. Other protocols that include left ventricular stimulation sites, isoproterenol infusion, use of quadruple extrastimuli, and the addition of long-short pacing cycle length induction, may have different day-to-day variability. The patients receiving antiarrhythmic agents underwent the first PES studies after 4 doses, while the second PES study may have been performed at a more steady-state level. The effect of additional days of amiodarone may also affect PES-2 response. Since no drug levels were drawn, this may account for some variability in the PES responses. Our patient population was heterogeneous and was intended to be that way in order to study the reproducibility of electrophysiologic studies done in a typical electrophysiology laboratory.

Clinical implications: Our study demonstrates that in patients with and without coronary artery disease there are certain PES responses that are more reproducible than others. Inducible sustained monomorphic VT and no inducible sustained VT were very reproducible. However, PES end points of nonsustained VT, polymorphic VT and rapid VT (rate ≥250 beats/min), were not very reproducible; these end points may not be adequate to guide therapy in this high-risk population. The end point of sustained monomorphic VT, especially when slow (rate <250 beats/min) is reproducible and can be used to guide antiarrhythmic therapy.

Acknowledgment: We acknowledge the expert secretarial assistance of Sharon Hines.

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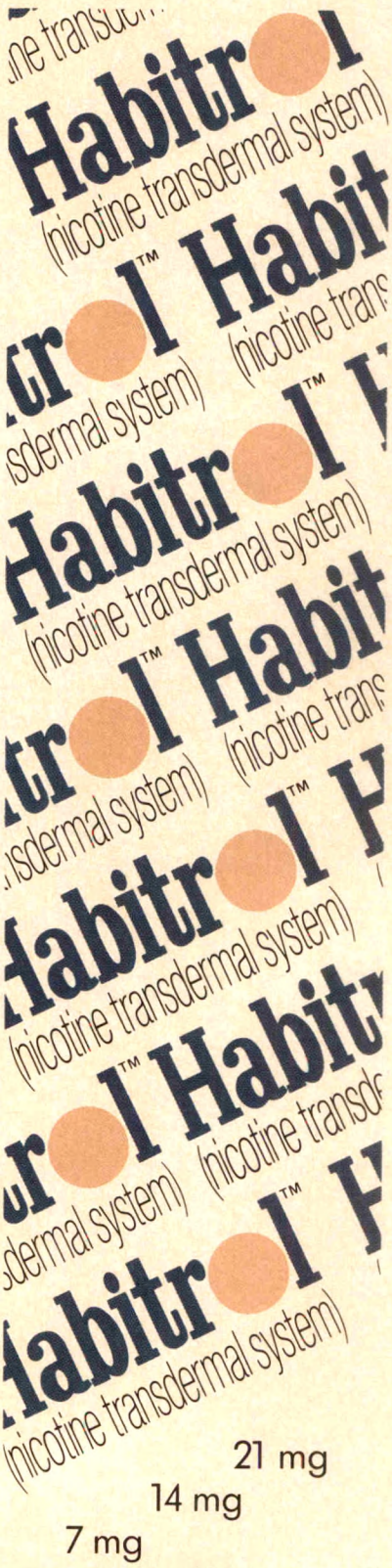
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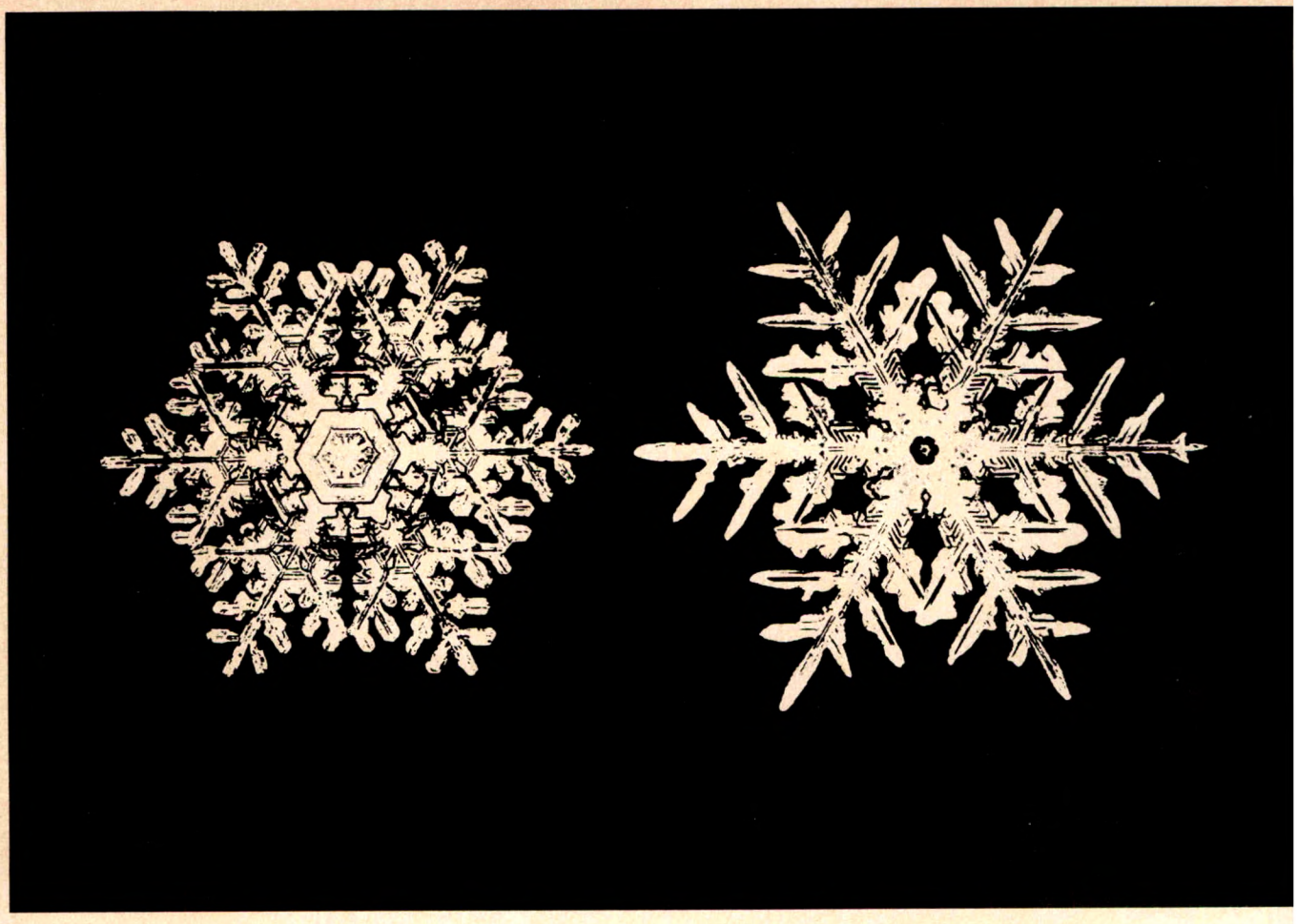
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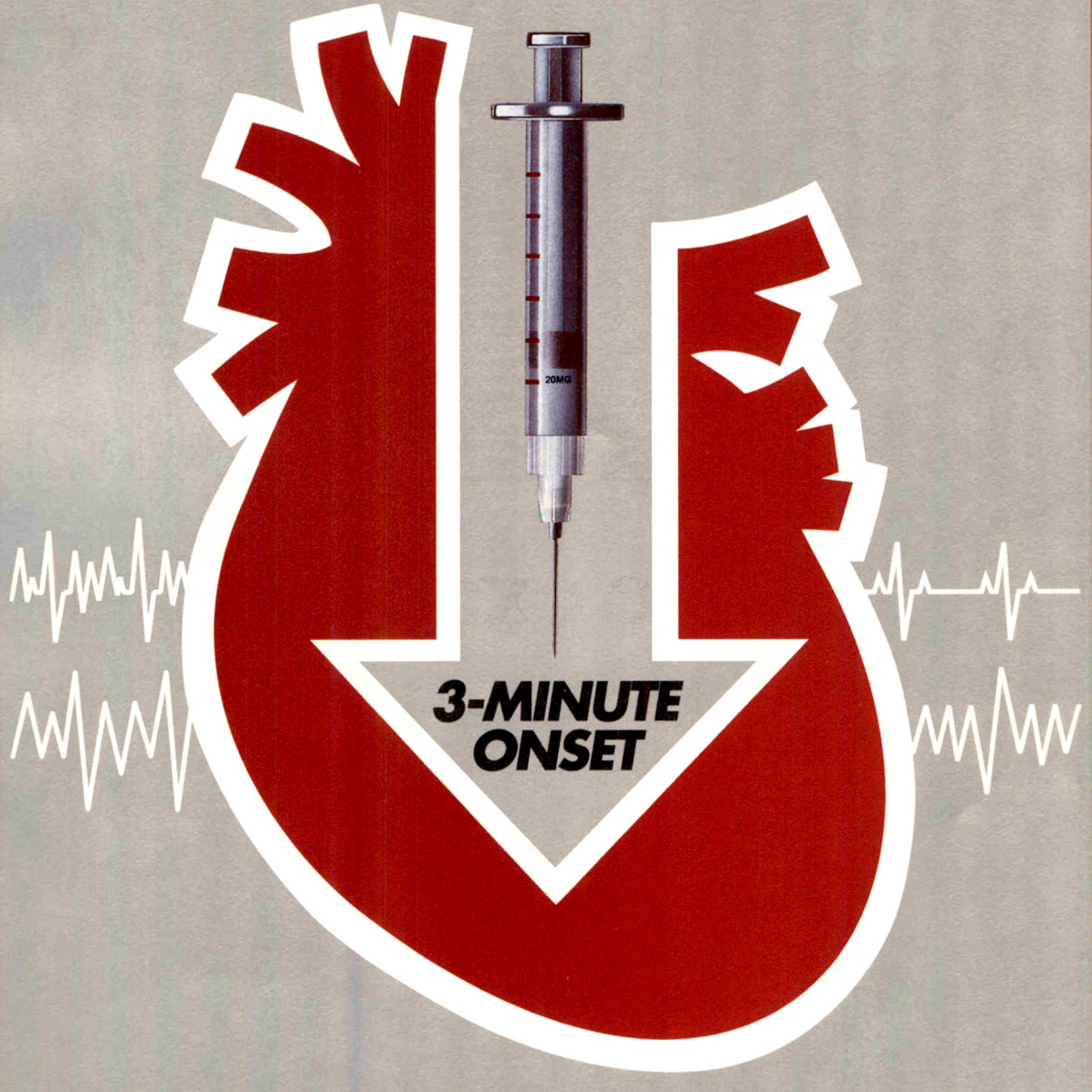
IF A NEW MEDICINE CAN HELP, WE'RE WORKING ON IT.

Now for heart rate control during atrial fibrillation and flutter

CARDIZEM® 5 mg/mL Injectable

(diltiazem hydrochloride)

BOLUS / INFUSION



GAINS HEART RATE CONTROL QUICKLY...

CIVAH495/A8113

Cardizem Injectable is indicated for temporary control of rapid ventricular rate during atrial fibrillation and flutter; rarely converts to normal sinus rhythm.

Please see the brief summary of prescribing information on an adjacent page.

6493E2

CARDIZEM® Injectable
(diltiazem hydrochloride)
BOLUS INFUSION



Should be used with continuous monitoring of ECG and blood pressure to avoid hypotension or bradycardia. Infusion rate/dose should be regulated accordingly. A defibrillator and emergency equipment should be readily available.

CIVAH495/A8113

For heart rate control during atrial fibrillation and flutter

MAINTAINS HEART RATE CONTROL SAFELY

FAST

- 3-minute onset of action from first bolus injection[1]
- 95% response rate within 2 to 7 minutes of administration[1]
- 1- to 3-hour duration of action with bolus

SAFE

- 4.3% incidence of asymptomatic hypotension[1]*
- 3.2 % incidence of symptomatic hypotension[1]*
- 3.9% incidence of injection site reaction[1]
- 1.7% incidence of flushing[1]*
- Little negative inotropic effect[1†]
- Do not use in Af/Fl patients with WPW or short PR syndrome

  Other contraindications: sick sinus syndrome and second- or third-degree AV block except with a functioning pacemaker; severe hypotension and shock; hypersensitivity; recent IV beta-blockers; ventricular tachycardia.

CONTINUOUS CONTROL

- Heart rate control through infusion for up to 24 hours[1,2]

  Cardizem Injectable is indicated for temporary control of rapid ventricular rate during atrial fibrillation and flutter; rarely converts to normal sinus rhythm.

*Occurs most often during or immediately following bolus injection.
†Caution should be used in patients with congestive heart failure.

CARDIZEM INJECTABLE
Heart rate control that is fast, safe, and continuous

Please see the brief summary of prescribing information on an adjacent page.

6493E2

CARDIZEM® Injectable
(diltiazem hydrochloride)
BOLUS INFUSION

CONVENIENT DOSAGE

1	2	3
Beginning treatment as	If response is inadequate, wait 15 minutes	Treatment as
BOLUS: 0.25 mg/kg actual body weight over 2 minutes	**BOLUS:** 0.35 mg/kg actual body weight over 2 minutes	**INFUSION: 10* to 15 mg/hr** *5 mg/hr may be appropriate starting infusion for some patients.
20 mg average patient	**25 mg average patient**	

BRIEF SUMMARY

CARDIZEM® Injectable
(diltiazem hydrochloride)

INDICATIONS AND USAGE

CARDIZEM Injectable (diltiazem hydrochloride) is indicated for the following:

1. **Atrial Fibrillation or Atrial Flutter.** Temporary control of rapid ventricular rate in atrial fibrillation or atrial flutter. It should not be used in patients with atrial fibrillation or atrial flutter associated with an accessory bypass tract such as in Wolff-Parkinson-White (WPW) syndrome or short PR syndrome.
2. **Paroxysmal Supraventricular Tachycardia.** Rapid conversion of paroxysmal supraventricular tachycardias (PSVT) to sinus rhythm. This includes AV nodal reentrant tachycardias and reciprocating tachycardias associated with an extranodal accessory pathway such as the WPW syndrome or short PR syndrome. Unless otherwise contraindicated, appropriate vagal maneuvers should be attempted prior to administration of CARDIZEM Injectable.

The use of CARDIZEM Injectable for control of ventricular response in patients with atrial fibrillation or atrial flutter or conversion to sinus rhythm in patients with PSVT should be undertaken with caution when the patient is compromised hemodynamically or is taking other drugs that decrease any or all of the following: peripheral resistance, myocardial filling, myocardial contractility, or electrical impulse propagation in the myocardium.

For either indication and particularly when employing continuous intravenous infusion, the setting should include continuous monitoring of the ECG and frequent measurement of blood pressure. A defibrillator and emergency equipment should be readily available.

In domestic controlled trials in patients with atrial fibrillation or atrial flutter, bolus administration of CARDIZEM Injectable was effective in reducing heart rate by at least 20% in 95% of patients. CARDIZEM Injectable rarely converts atrial fibrillation or atrial flutter to normal sinus rhythm. Following administration of one or two intravenous bolus doses of CARDIZEM Injectable, response usually occurs within 3 minutes and maximal heart rate reduction generally occurs in 2 to 7 minutes. Heart rate reduction may last from 1 to 3 hours. If hypotension occurs, it is generally short-lived, but may last from 1 to 3 hours.

A 24-hour continuous infusion of CARDIZEM Injectable in the treatment of atrial fibrillation or atrial flutter maintained at least a 20% heart rate reduction during the infusion in 83% of patients. Upon discontinuation of infusion, heart rate reduction may last from 0.5 hours to more than 10 hours (median duration 7 hours). Hypotension, if it occurs, may be similarly persistent.

In the controlled clinical trials, 3.2% of patients required some form of intervention (typically, use of intravenous fluids or the Trendelenburg position) for blood pressure support following CARDIZEM Injectable.

In domestic controlled trials, bolus administration of CARDIZEM Injectable was effective in converting PSVT to normal sinus rhythm in 88% of patients within 3 minutes of the first or second bolus dose.

Symptoms associated with the arrhythmia were improved in conjunction with decreased heart rate or conversion to normal sinus rhythm following administration of CARDIZEM Injectable.

CONTRAINDICATIONS

CARDIZEM Injectable is contraindicated in:

1. Patients with sick sinus syndrome except in the presence of a functioning ventricular pacemaker.
2. Patients with second- or third-degree AV block except in the presence of a functioning ventricular pacemaker.
3. Patients with severe hypotension or cardiogenic shock.
4. Patients who have demonstrated hypersensitivity to the drug.
5. Intravenous diltiazem and intravenous beta-blockers should not be administered together or in close proximity (within a few hours).
6. Patients with atrial fibrillation or atrial flutter associated with an accessory bypass tract such as in WPW syndrome or short PR syndrome.

   As with other agents which slow AV nodal conduction and do not prolong the refractoriness of the accessory pathway (eg, verapamil, digoxin), in rare instances patients in atrial fibrillation or atrial flutter associated with an accessory bypass tract may experience a potentially life-threatening increase in heart rate accompanied by hypotension when treated with CARDIZEM Injectable. As such, the initial use of CARDIZEM Injectable should be, if possible, in a setting where monitoring and resuscitation capabilities, including DC cardioversion/defibrillation, are present (see OVERDOSAGE). Once familiarity of the patient's response is established, use in an office setting may be acceptable.
7. Patients with ventricular tachycardia. Administration of other calcium channel blockers to patients with wide complex tachycardia (QRS $\geq$ 0.12 seconds) has resulted in hemodynamic deterioration and ventricular fibrillation. It is important that an accurate pretreatment diagnosis distinguish wide complex QRS tachycardia of supraventricular origin from that of ventricular origin prior to administration of CARDIZEM Injectable.

WARNINGS

1. **Cardiac Conduction.** Diltiazem prolongs AV nodal conduction and refractoriness that may rarely result in second- or third-degree AV block in sinus rhythm. Concomitant use of diltiazem with agents known to affect cardiac conduction may result in additive effects (see Drug Interactions). If high-degree AV block occurs in sinus rhythm, intravenous diltiazem should be discontinued and appropriate supportive measures instituted (see OVERDOSAGE).
2. **Congestive Heart Failure.** Although diltiazem has a negative inotropic effect in isolated animal tissue preparations, hemodynamic studies in humans with normal ventricular function and in patients with a compromised myocardium, such as severe CHF, acute MI, and hypertrophic cardiomyopathy, have not shown a reduction in cardiac index nor consistent negative effects on contractility (dp/dt). Administration of oral diltiazem in patients with acute myocardial infarction and pulmonary congestion documented by x-ray on admission is contraindicated. Experience with the use of CARDIZEM Injectable in patients with impaired ventricular function is limited. Caution should be exercised when using the drug in such patients.
3. **Hypotension.** Decreases in blood pressure associated with CARDIZEM Injectable therapy may occasionally result in symptomatic hypotension (3.2%). The use of intravenous diltiazem for control of ventricular response in patients with supraventricular arrhythmias should be undertaken with caution when the patient is compromised hemodynamically. In addition, caution should be used in patients taking other drugs that decrease peripheral resistance, intravascular volume, myocardial contractility or conduction.
4. **Acute Hepatic Injury.** In rare instances, significant elevations in enzymes such as alkaline phosphatase, LDH, SGOT, SGPT, and other phenomena consistent with acute hepatic injury have been noted following oral diltiazem. Therefore, the potential for acute hepatic injury exists following administration of intravenous diltiazem.
5. **Ventricular Premature Beats (VPBs).** VPBs may be present on conversion of PSVT to sinus rhythm with CARDIZEM Injectable. These VPBs are transient, are typically considered to be benign, and appear to have no clinical significance. Similar ventricular complexes have been noted during cardioversion, other pharmacologic therapy, and during spontaneous conversion of PSVT to sinus rhythm.

PRECAUTIONS

General. CARDIZEM (diltiazem hydrochloride) is extensively metabolized by the liver and excreted by the kidneys and in bile. The drug should be used with caution in patients with impaired renal or hepatic function (see WARNINGS). High intravenous dosages (4.5 mg/kg tid) administered to dogs resulted in significant bradycardia and alterations in AV conduction. In subacute and chronic dog and rat studies designed to produce toxicity, high oral doses of diltiazem were associated with hepatic damage. In special subacute hepatic studies, oral doses of 125 mg/kg and higher in rats were associated with histological changes in the liver, which were reversible when the drug was discontinued. In dogs, oral doses of 20 mg/kg were also associated with hepatic changes; however, these changes were reversible with continued dosing.

Dermatologic events progressing to erythema multiforme and/or exfoliative dermatitis have been infrequently reported following oral diltiazem. Therefore, the potential for these dermatologic reactions exists following exposure to intravenous diltiazem. Should a dermatologic reaction persist, the drug should be discontinued.

Drug Interactions. Due to potential for additive effects, caution is warranted in patients receiving CARDIZEM Injectable concomitantly with any agent(s) known to affect cardiac contractility and/or SA or AV node conduction (see WARNINGS).

As with all drugs, care should be exercised when treating patients with multiple medications. CARDIZEM undergoes extensive metabolism by the cytochrome P-450 mixed function oxidase system. Although specific pharmacokinetic drug-drug interaction studies have not been conducted with single intravenous injection or constant rate intravenous infusion, coadministration of CARDIZEM Injectable with other agents which primarily undergo the same route of biotransformation may result in competitive inhibition of metabolism.

Digitalis: Intravenous diltiazem has been administered to patients receiving either intravenous or oral digitalis therapy. The combination of the two drugs was well tolerated without serious adverse effects. However, since both drugs affect AV nodal conduction, patients should be monitored for excessive slowing of the heart rate and/or AV block.

Beta-blockers: Intravenous diltiazem has been administered to patients on chronic oral beta-blocker therapy. The combination of the two drugs was generally well tolerated without serious adverse effects. If intravenous diltiazem is administered to patients receiving chronic oral beta-blocker therapy, the possibility for bradycardia, AV block, and/or depression of contractility should be considered (see CONTRAINDICATIONS). ***Oral*** administration of diltiazem with propranolol in five normal volunteers resulted in increased propranolol levels in all subjects and bioavailability of propranolol was increased approximately 50%. In vitro, propranolol appears to be displaced from its binding sites by diltiazem.

Anesthetics: The depression of cardiac contractility, conductivity, and automaticity as well as the vascular dilation associated with anesthetics may be potentiated by calcium channel blockers. When used concomitantly, anesthetics and calcium blockers should be titrated carefully.

Carcinogenesis, Mutagenesis, Impairment of Fertility. A 24-month study in rats at oral dosage levels of up to 100 mg/kg/day, and a 21-month study in mice at oral dosage levels of up to 30 mg/kg/day showed no evidence of carcinogenicity. There was also no mutagenic response in vitro or in vivo in mammalian cell assays or in vitro in bacteria. No evidence of impaired fertility was observed in a study performed in male and female rats at oral dosages of up to 100 mg/kg/day.

Pregnancy. Category C. Reproduction studies have been conducted in mice, rats, and rabbits. Administration of oral doses ranging from five to ten times greater (on a mg/kg basis) than the daily recommended oral antianginal therapeutic dose has resulted in embryo and fetal lethality. These doses, in some studies, have been reported to cause skeletal abnormalities. In the perinatal/postnatal studies there was some reduction in early individual pup weights and survival rates. There was an increased incidence of stillbirths at doses of 20 times the human oral antianginal dose or greater.

There are no well-controlled studies in pregnant women; therefore, use CARDIZEM in pregnant women only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers. Diltiazem is excreted in human milk. One report with oral diltiazem suggests that concentrations in breast milk may approximate serum levels. If use of CARDIZEM is deemed essential, an alternative method of infant feeding should be instituted.

Pediatric Use. Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

The following adverse reaction rates are based on the use of CARDIZEM Injectable in over 400 domestic clinical trial patients with atrial fibrillation/flutter or PSVT under double-blind or open-label conditions. Worldwide experience in over 1,300 patients was similar.

Adverse events reported in controlled and uncontrolled clinical trials were generally mild and transient. Hypotension was the most commonly reported adverse event during clinical trials. Asymptomatic hypotension occurred in 4.3% of patients. Symptomatic hypotension occurred in 3.2% of patients. When treatment for hypotension was required, it generally consisted of administration of saline or placing the patient in the Trendelenburg position. Other events reported in at least 1% of the diltiazem-treated patients were injection site reactions (eg, itching, burning)—3.9%, vasodilation (flushing)—1.7%, and arrhythmia (junctional rhythm or isorhythmic dissociation)—1.0%.

In addition, the following events were reported infrequently (less than 1%):

Cardiovascular:	Atrial flutter, AV block first degree, AV block second degree, bradycardia, chest pain, congestive heart failure, sinus pause, sinus node dysfunction, syncope, ventricular arrhythmia, ventricular fibrillation, ventricular tachycardia.
Dermatologic:	Pruritus, sweating.
Gastrointestinal:	Constipation, elevated SGOT or alkaline phosphatase, nausea, vomiting.
Nervous System:	Dizziness, paresthesia.
Other:	Amblyopia, asthenia, dry mouth, dyspnea, edema, headache, hyperuricemia.

Although not observed in clinical trials with CARDIZEM Injectable, other reactions associated with oral diltiazem may occur.

Product information as of October 1991

References: 1. Cardizem Injectable prescribing information. 2. Ellenbogen KA, Dias VC, Plumb VJ, Heywood JT, Mirvis DM. *J Am Coll Cardiol.* 1991;18:891-897.

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CARDIZEM INJECTABLE...HEART RATE CONTROL THAT IS FAST, SAFE, AND CONTINUOUS

Late Ventricular Arrhythmia and Sudden Death Following Direct-Current Catheter Ablation of the Atrioventricular Junction

James C. Perry, MD, Debra L. Kearney, MD, Richard A. Friedman, MD, Jeffrey P. Moak, MD, and Arthur Garson, Jr., MD

Early reports of direct-current catheter ablation (DCCA) of the atrioventricular (AV) junction for resistant AV tachycardias documented efficacy of DCCA with little morbidity. Nine patients underwent DCCA at our institution 4 to 9 years ago: 3 patients had DCCA in the coronary sinus for permanent junctional reciprocating tachycardia, 2 patients had His ablation, 2 had coronary sinus and His ablation for permanent junctional reciprocating tachycardia, and 2 had DCCA for congenital junctional ectopic tachycardia. Shocks (total 1 to 5) ranged from 12.5 to 400 J. Five patients had pacemaker implant at the time of DCCA. During follow-up, 3 patients developed clinical ventricular tachycardia: all 3 had DCCA of the His bundle. One asymptomatic patient with ventricular tachycardia, who had DCCA of the bundle of His, died suddenly 6 years later with ventricular fibrillation. Autopsy revealed 2 ventricular scars: 1 extending from the AV junction and 1 in the outflow tract. No patient with DCCA limited to the coronary sinus developed ventricular tachycardia. DCCA of the His bundle can result in late ventricular arrhythmias, possibly a result of extension of the DCCA lesion into the ventricle. These late findings should be considered in evaluating the safety and efficacy and follow-up for patients undergoing radiofrequency ablation.

(Am J Cardiol 1992;70:765–768)

Direct-current catheter ablation (DCCA) techniques were developed in the late 1970s as a nonpharmacologic means of managing resistant arrhythmias.[1] The first reports on the use of DCCA in adult patients appeared in the early 1980s.[2,3] In these reports, DCCA was performed in the region of the bundle of His in patients with refractory atrial tachyarrhythmias. The procedure was successful in producing complete atrioventricular (AV) block in 70 to 90% of patients, thereby reducing ventricular rate and allowing either ventricular demand or rate-responsive pacing.[4,5]

In addition to the desired electrophysiologic effects, nonsustained ventricular arrhythmias and sudden death were seen in the early postablation period in some patients.[4,5] Recently, the long-term follow-up of patients who underwent DCCA with a mean duration of follow-up of 41 months showed no significant, late-appearing arrhythmias.[6]

Reports on the use of DCCA in children appeared in the mid-1980s.[7,8] Over the last 1 to 2 years, we began to note apparent late ventricular arrhythmias in some of our patients who had undergone DCCA of the AV junction. This review was undertaken to investigate the long-term follow-up of these patients.

METHODS

A retrospective review of all patients was performed by analysis of the hospital and catheterization records at Texas Children's Hospital. Every patient who had DCCA of the AV junction was included in the study.

Patient records were reviewed for the following variables: age of the patient at diagnosis and at the time of DCCA, cardiac anatomic and electrophysiologic diagnoses, the intracardiac location of catheter ablation, energy delivered at ablation (expressed as the maximal and cumulative watt-seconds (W-s) per kilogram), several applications, initial success rate, status of AV and ventriculoatrial conduction after ablation, and type of pacing system, if any, implanted after ablation. Duration of follow-up was noted, as well as symptoms related to the underlying structural cardiac abnormality or arrhythmia. All follow-up laboratory data were analyzed; all patients had surface electrocardiograms and treadmill exams.

One patient died suddenly. Pathologic examination of the heart was performed at Texas Children's Hospital. In addition to random atrial and ventricular sections, specific sections were taken from areas of the heart pertaining to the DCCA procedures to include the AV node through the proximal bundle branches. The tissues were processed by routine histologic techniques and, with the exception of the conduction tissue sec-

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TABLE I Diagnoses and Direct-Current Ablation Data

Dx	Pt.	Age (yr)	Ablation Site	Shocks	W-s/kg Max.	W-s/kg Cum.	Success
1	PJRT	8	MOCS	3	1.8	4.6	+
2		2.5	MOCS	2	3.6	5.8	0
3		3	MOCS	1	6.6	6.6	+
4		10.5	MOCS/His	8	9.4	51.6	+
5	Atyp. AVN	27	His	3	1.4	2.5	+
6	PO WPW	17	His	2	2.8	5.5	+
7		17	His	3	6.2	12.5	+
8	Cong. JET	10/12	His	4	2.7	9.6	+
9		6/12	His	3	4.2	8.8	+

Atyp. AVN = atypical atrioventricular node reentry tachycardia; Cong. JET = congenital junctional ectopic tachycardia; Cum. = cumulative; Dx = diagnosis; Max. = maximal; MOCS = mouth of the coronary sinus; PJRT = permanent junctional reciprocating tachycardia; PO WPW = postoperative Wolff-Parkinson-White syndrome; + = successful; 0 = not successful.

TABLE II Atrioventricular Conduction and Pacemaker Data After Direct-Current Ablation

Pt.	Ablation Site	Conduction AV	Conduction VA	Pacing Mode	PMT
1	MOCS	0	+	DDD	+
2	MOCS	+	+	None	—
3	MOCS	0	+	DDD	+
4	MOCS/His	0	+	DDD	+
5	His	0	+	DDD*	+*
6	His	0	+	DDD	+
7	His	0	0	DDD	0
8	His	+	0	DDD	0
9	His	0	0	DDD	0

*Patients initially had a VVI pacing system.
AV = atrioventricular; MOCS = mouth of the coronary sinus; PMT = pacemaker-mediated tachycardia; VA = ventriculoatrial; 0 = not present; + = present.

tions, the slides were stained with hematoxylin and eosin. The right ventricular outflow tract was also examined with a modified Gomori's trichrome stain. Each of the 5 paraffin blocks from the conduction system were sectioned serially and at least every 20th section was examined microscopically with a modified Gomori's trichrome stain.

Where appropriate, comparison of data between patients with and without postablation ventricular arrhythmias was done using chi-square analysis.

RESULTS

Patient demographics: Nine patients underwent DCCA of the AV junction at Texas Children's Hospital. The ablations were performed between August 1982 and December 1987. Seven of the patients had ablation performed in the 12-month period from August 1982 to July 1983. The patient ages at the time of DCCA ranged from 6 months to 27 years (1 patient was >17 years old, mean 9.6 years).

Electrophysiologic study: All 9 patients had intracardiac electrophysiologic study performed at the time of DCCA (Table I). The diagnoses before DCCA were: permanent form of junctional reciprocating tachycardia in 4 patients, atypical AV node reentry tachycardia in 1, Wolff-Parkinson-White syndrome after surgery in 2 patients, and congenital junctional ectopic tachycardia in 1 infant.

Direct-current catheter ablation: After electrophysiologic determination of the underlying mechanism of the tachycardia, DCCA was performed. In all cases, a tripolar or quadripolar catheter was positioned in the desired location and connected to a standard cardioverter-defibrillator energy source. A grounding patch was placed below the patient's left scapula to function as the cathode and an electrode pair was chosen on the intracardiac recording catheter as the anode. Energy output ranged from 12.5 to 300 W-s depending on patient size. For patients with permanent junctional reciprocating tachycardia, the mouth of the coronary sinus was the initial ablation site. Patients with atypical AV node reentrant tachycardia and congenital junctional ectopic tachycardia, and those who had undergone unsuccessful surgery for Wolff-Parkinson-White syndrome underwent elective His-bundle ablation at the site of the largest His-bundle deflection.

The number of shocks delivered ranged from 1 to 8. The maximal single shock energy given ranged from 1.4 to 9.4 W-s/kg and the cumulative shock energy was 2.5 to 51.5 W-s/kg.

Initial success was obtained in 7 of 9 patients (78%). Immediately after application of DCCA, 5 of the 9 patients experienced a slow ventricular escape rhythm. One child with congenital junctional tachycardia had ventricular fibrillation after the initial ablation and required resuscitation. Subsequent ablations of the bundle of His in this patient resulted in sinus rhythm with first-degree AV block and complete right bundle branch block.

Pacemaker implantation: Eight of 9 patients underwent pacemaker implantation either at the time of DCCA or within 2 days (Table II). All 8 currently have dual-chambered pacing systems. Each of the 4 patients with residual, slow retrograde conduction after the ablation experienced subsequent episodes of pacemaker-mediated tachycardia.

Ventricular arrhythmias: Three of the 9 patients developed late ventricular arrhythmias. The interval from ablation to first detection of these arrhythmias ranged from 3 to 7 years (mean 53 months). Each of these 3 patients had His-bundle ablations; none had ablations performed solely at the mouth of the coronary sinus. One patient had a dilated cardiomyopathic picture at the time of ablation (patient 4) and 2 had undergone accessory pathway surgery before ablation. There were no differences between these 3 patients and the 6 patients who did not developed ventricular arrhythmias with respect to maximal or cumulative energy delivered. The duration of follow-up for the 3 patients with ventricular arrhythmias was actually shorter (5.9 ± 1.6 years) than the 5 patients who did not have ventricular arrhythmias (8.8 ± 0.7 years, $p < 0.01$).

Of the 3 patients with late ventricular arrhythmias, all 3 had monomorphic ventricular tachycardia. In each, ventricular tachycardia was exercise-induced and provoked during treadmill testing. Two patients had spontaneous ventricular tachycardia with exertion during ambulatory Holter monitoring. The rates of ventricular tachycardia ranged from 110 to 165 beats/min. Although a ventricular tachycardia rate of 110 beats/min

is "slow VT," it occurred when the sinus rate was 60 beats/min immediately after exercise. One patient had ventricular tachycardia with left bundle branch block morphology, and the other 2 had right bundle branch block with normal initial QRS-segment axis.

Two of the patients with ventricular tachycardia experienced palpitations and 1 had near-syncope associated with runs of nonsustained ventricular tachycardia. Patient 4 had not complained of symptoms before sudden death.

Sudden death: Sudden death occurred in a 16½-year-old patient (no. 4) who presented at age 10 years with dilated cardiomyopathy secondary to incessant tachycardia.

At the first DCCA session, 150 W-s of energy was delivered to the mouth of the coronary sinus, but tachycardia recurred 2 days later. A second DCCA delivered a slightly higher energy dose (200 W-s), but supraventricular tachycardia recurred. The third DCCA consisted of successful His-bundle ablation (150 W-s twice followed by 200 W-s twice) and implantation of a DDD pacing system. Slow retrograde conduction was still intact, and the post-DCCA course was complicated by pacemaker-mediated tachycardia. Six months later, during a fourth session, 2 high energy shocks (300 W-s each) were delivered with successful elimination of retrograde conduction. This was followed by appropriate DDD pacemaker function. After the last DCCA, this patient had persistently elevated left ventricular end-diastolic dimensions ranging from 47 to 70 mm. Four years after the last ablation, he developed exercise-induced left bundle branch block morphology ventricular tachycardia at 110 to 148 beats/min. He had been taking digoxin, and mexiletine was added. Over the next 2 years, ventricular ectopy decreased and no ventricular tachycardia was present on treadmill or 24-hour Holter monitoring. His left ventricular end-diastolic diameter was measured as 60 mm. While playing tennis, he had an arrest. Ventricular fibrillation was documented within minutes of his collapse.

Autopsy findings: The heart was enlarged with moderate to marked dilation of both ventricular chambers and moderately hypertrophied myofibers. The 2

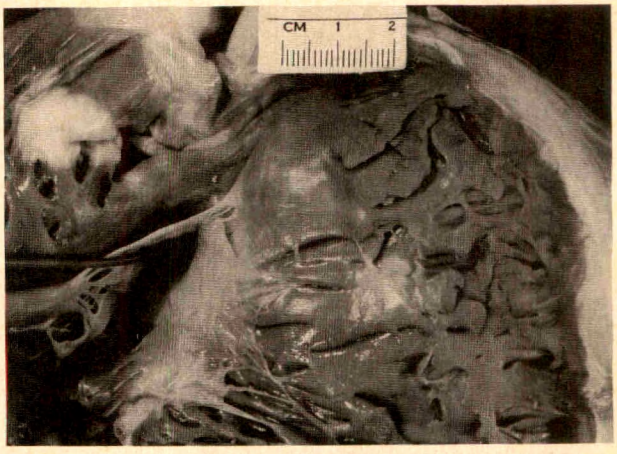


FIGURE 1. The septal surface of the right ventricle is exposed with the tricuspid valve and free wall reflected to the *left* and the pulmonary valve *above*. Three areas of *grey-white fibrous scarring* are visible: one extending from the tricuspid annulus beneath the septal leaflet, another in the free wall of the outflow tract with the orifice of an aneurysmal pouch situated between it and the pulmonary valve, and the third on the midtrabecular ventricular septum.

TABLE III Comparison of Tissue Effects, Direct-Current Ablation Versus Radiofrequency Ablation

	Direct-Current	Radiofrequency
Mode of injury	trauma, hemorrhage	Dessication, coagulation necrosis
Border zone	Often irregular, heterogeneous	More homogeneous
Lesion size	5–20 mm	3–6 mm
Shape	Variable, stellate	More spherical

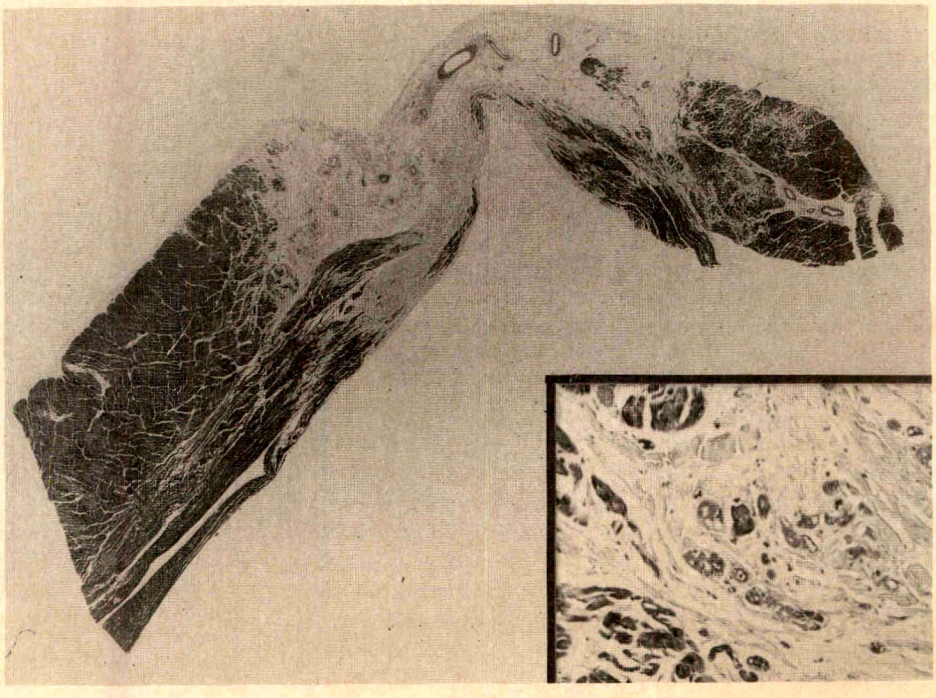


FIGURE 2. This transmural section is taken through the aneurysmal scar in the right ventricular outflow tract. The myocardial wall is thinned and composed of collagen, variably-sized blood vessels and paler staining adipose tissue. The border with the adjacent myocardium is irregular with scattered islands of entrapped myocytes (insert). (Gomori's trichrome ×5, inset ×130, reduced by 25%.)

transvenous pacemaker leads were embedded within the endocardium. In the anterior free wall of the right ventricular outflow tract a circumscribed area of transmural fibrous scarring was associated with thinning of the wall, forming a 2.0 × 1.0 cm aneurysmal pouch (Figure 1). Fibrous scarring was also grossly apparent in the region of the AV node extending into the contiguous crest of the ventricular septum and confluent with the membranous septum.

Microscopically, the ventricular myocardium as a whole demonstrated features of hypertrophy but no significant degenerative changes and minimal scarring. Contraction band necrosis, consistent with terminal ventricular fibrillation, was widely dispersed throughout both ventricles. The right ventricular outflow tract scar was composed of loose and dense fibrous tissue with admixed adipose tissue (Figure 2). At the border zones of scar tissue with adjacent myocardium, small islands of residual myocytes were entrapped within the scar (Figure 2, insert).

The sections of the conduction system revealed extensive fibrofatty replacement of the AV node and contiguous base of the atrial septum with obliteration of the atrial approaches to the node. Only a residual portion of the deep atrial septal extent of the AV node persisted. Dense collagenous scar tissue replaced many of the right ventricular myofibers at the crest of the ventricular septum. Essentially no fibers of the bundle of His were recognizable. Patchy scarring continued into the distal branching bundle and proximal bundle branches with intermittent segments of complete fibrous obliteration. The ventricular septal scarring increased along the length of the conduction system axis so that beneath the membranous septum (distal branching bundle) the septal crest was markedly thinned and fibrotic with the left ventricular aspect as affected as the right side.

DISCUSSION

Although early results of DCCA of the AV junction were encouraging, some patients have had ventricular arrhythmias soon after ablation.[4,5] This report shows that significant, potentially life-threatening ventricular tachycardia may occur many years after DCCA.

Recently, radiofrequency current has become a preferred method for transcatheter ablation of arrhythmogenic substrates.[9–11] There are several potential benefits of radiofrequency ablation over direct-current techniques. A comparison of the 2 techniques is shown in Table III. Radiofrequency ablation results in coagulation necrosis and dessication, and avoids the barotrauma and hemorrhage that frequently occurs with DCCA. Radiofrequency ablation results in a more homogeneous scar and more distinct scar-tissue "border zones," smaller and more "controllable" lesions, and more circular lesions than direct-current applications.[12]

Radiofrequency ablation has already proved its value in eliminating atrial ectopic, junctional,[11] AV reciprocating[9,10] and some ventricular tachycardias,[13] as well as elective ablation of the bundle of His.[14] Although early results of radiofrequency ablation are encouraging, follow-up does not extend beyond 2 years for most institutions.

Autonomic control: Changes in autonomic cardiovascular control may occur in early puberty and adolescence,[15] thereby having an influence on arrhythmogenesis in the border zone of direct-current scars. A change in the adrenergic receptor population in the border zone region of myocardial infarction has been documented previously.[16] Ventricular tachycardia in our patients was exercise-induced, lending some support to the notion of altered adrenergic control in the region of the scar.

Comment: The findings in this review should be addressed in the long-term follow-up of patients after both direct-current and radiofrequency ablation, especially when the ablation site includes the AV node or the ventricular myocardial insertion points of accessory connections. Follow-up should continue for several years after the procedure, well into adulthood for those who underwent ablation before puberty, and should include treadmill testing to screen for exercise-induced arrhythmias.

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CARDURA® (doxazosin mesylate) Tablets
Brief Summary of Prescribing Information

INDICATIONS AND USAGE

CARDURA (doxazosin mesylate) is indicated for the treatment of hypertension. CARDURA may be used alone or in combination with diuretics or beta-adrenergic blocking agents. There is limited experience with CARDURA in combination with angiotensin converting enzyme inhibitors or calcium channel blockers.

CONTRAINDICATIONS

CARDURA is contraindicated in patients with a known sensitivity to quinazolines (e.g. prazosin, terazosin).

WARNINGS

Syncope and "First-dose" Effect:

Doxazosin, like other alpha-adrenergic blocking agents, can cause marked hypotension, especially in the upright position, with syncope and other postural symptoms such as dizziness. Marked orthostatic effects are most common with the first dose but can also occur when there is a dosage increase, or if therapy is interrupted for more than a few days. To decrease the likelihood of excessive hypotension and syncope, it is essential that treatment be initiated with the 1 mg dose. The 2, 4, and 8 mg tablets are not for initial therapy. Dosage should then be adjusted slowly (see DOSAGE AND ADMINISTRATION section) with increases in dose every two weeks. Additional antihypertensive agents should be added with caution.

Patients being titrated with doxazosin should be cautioned to avoid situations where injury could result should syncope occur.

In an early investigational study of the safety and tolerance of increasing daily doses of doxazosin in normotensives beginning at 1 mg/day, only 2 of 6 subjects could tolerate more than 2 mg/day without experiencing symptomatic postural hypotension. In another study of 24 healthy normotensive male subjects receiving initial doses of 2 mg/day of doxazosin, seven (29%) of the subjects experienced symptomatic postural hypotension between 0.5 and 6 hours after the first dose necessitating termination of the study. In this study 2 of the normotensive subjects experienced syncope. Subsequent trials in hypertensive patients always began doxazosin dosing at 1 mg/day resulting in a 4% incidence of postural side effects at 1 mg/day with no cases of syncope.

In multiple dose clinical trials involving over 1500 patients with dose titration every one to two weeks, syncope was reported in 0.7% of patients. None of these events occurred at the starting dose of 1 mg and 1.2% (8/664) occurred at 16 mg/day.

If syncope occurs, the patient should be placed in a recumbent position and treated supportively as necessary.

PRECAUTIONS

General

1. Orthostatic Hypotension:

While syncope is the most severe orthostatic effect of CARDURA, other symptoms of lowered blood pressure, such as dizziness, lightheadedness, or vertigo, can occur, especially at initiation of therapy or at the time of dose increases. These were common in clinical trials, occurring in up to 23% of all patients treated and causing discontinuation of therapy in about 2%.

In placebo controlled titration trials orthostatic effects were minimized by beginning therapy at 1 mg per day and titrating every two weeks to 2, 4, or 8 mg per day. There was an increased frequency of orthostatic effects in patients given 8 mg or more, 10%, compared to 5% at 1-4 mg and 3% in the placebo group.

Patients in occupations in which orthostatic hypotension could be dangerous should be treated with particular caution.

If hypotension occurs, the patient should be placed in the supine position and, if this measure is inadequate, volume expansion with intravenous fluids or vasopressor therapy may be used. A transient hypotensive response is not a contraindication to further doses of CARDURA.

2. Impaired liver function:

CARDURA should be administered with caution to patients with evidence of impaired hepatic function or to patients receiving drugs known to influence hepatic metabolism (see CLINICAL PHARMACOLOGY). There is no controlled clinical experience with CARDURA in patients with these conditions.

3. Leukopenia/Neutropenia:

Analysis of hematologic data from patients receiving CARDURA in controlled clinical trials showed that the mean WBC (N=474) and mean neutrophil counts (N=419) were decreased by 2.4% and 1.0% respectively, compared to placebo, a phenomenon seen with other alpha blocking drugs. A search through a data base of 2400 patients revealed 4 in which drug-related neutropenia could not be ruled out. Two had a single low value on the last day of treatment. Two had stable, non-progressive neutrophil counts in the 1000/mm³ range over periods of 20 and 40 weeks. In cases where follow-up was available the WBCs and neutrophil counts returned to normal after discontinuation of CARDURA. No patients became symptomatic as a result of the low WBC or neutrophil counts.

Information for Patients:

Patients should be made aware of the possibility of syncopal and orthostatic symptoms, especially at the initiation of therapy, and urged to avoid driving or hazardous tasks for 24 hours after the first dose, after a dosage increase, and after interruption of therapy when treatment is resumed. They should be cautioned to avoid situations where injury could result should syncope occur during initiation of doxazosin therapy. They should also be advised of the need to sit or lie down when symptoms of lowered blood pressure occur, although these symptoms are not always orthostatic, and to be careful when rising from a sitting or lying position. If dizziness, lightheadedness, or palpitations are bothersome they should be reported to the physician, so that dose adjustment can be considered. Patients should also be told that drowsiness or somnolence can occur with doxazosin, requiring caution in people who must drive or operate heavy machinery.

Drug Interactions:

Most (98%) of plasma doxazosin is protein bound. *In vitro* data in human plasma indicate that CARDURA has no effect on protein binding of digoxin, warfarin, phenytoin or indomethacin. There is no information on the effect of other highly plasma protein bound drugs on doxazosin binding. CARDURA has been administered without any evidence of an adverse drug interaction to patients receiving thiazide diuretics, beta blocking agents, and nonsteroidal anti-inflammatory drugs.

Drug/Laboratory test interactions:

None known.

Cardiac Toxicity in Animals:

An increased incidence of myocardial necrosis or fibrosis was displayed by Sprague-Dawley rats after 6 months of dietary administration at concentrations calculated to provide 80 mg doxazosin/kg/day and after 12 months of dietary administration at concentrations calculated to provide 40 mg doxazosin/kg/day (150 times the maximum recommended human dose assuming a patient weight of 60 kg). Myocardial fibrosis was observed in both rats and mice treated in the same manner with 40 mg doxazosin/kg/day for 18 months. No cardiotoxicity was observed at lower doses (up to 10 or 20 mg/kg/day, depending on the study) in either species. These lesions were not observed after 12 months of oral dosing in dogs and Wistar rats at maximum doses of 20 mg/kg/day and 100 mg/kg/day, respectively. There is no evidence that similar lesions occur in humans.

Carcinogenesis, Mutagenesis and Impairment of Fertility:

Chronic dietary administration (up to 24 months) of doxazosin mesylate at maximally tolerated concentrations (highest dose 40 mg/kg: about 150 times the maximum recommended human dose of 16 mg/60 kg) revealed no evidence of carcinogenicity in rats. There was also no evidence of carcinogenicity in a similarly conducted study (up to 18 months of dietary administration) in mice. The mouse study, however, was compromised by the failure to use a maximally tolerated dose of doxazosin.

Mutagenicity studies revealed no drug- or metabolite-related effects at either chromosomal or subchromosomal levels.

Studies in rats showed reduced fertility in males treated with doxazosin at oral doses of 20 (but not 5 or 10) mg/kg/day, about 75 times the maximum recommended human dose. This effect was reversible within two weeks of drug withdrawal.

Pregnancy

Teratogenic Effects, Pregnancy Category B. Studies in rabbits and rats at daily oral doses of up to 40 and 20 mg/kg, respectively (150 and 75 times the maximum recommended daily dose of 16 mg, assuming a patient weight of 60 kg), have revealed no evidence of harm to the fetus. The rabbit study, however, was compromised by the failure to use a maximally tolerated dose of doxazosin. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, CARDURA should be used during pregnancy only if clearly needed.

Radioactivity was found to cross the placenta following oral administration of labelled doxazosin to pregnant rats.

Nonteratogenic Effects. In peri-postnatal studies in rats, postnatal development at maternal doses of 40 or 50 mg/kg/day of doxazosin was delayed as evidenced by slower body weight gain and a slightly later appearance of anatomical features and reflexes.

Nursing Mothers

Studies in lactating rats given a single oral dose of 1 mg/kg of [2-¹⁴C]-doxazosin indicate that doxazosin accumulates in rat breast milk with a maximum concentration about 20 times greater than the maternal plasma concentration. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when CARDURA is administered to a nursing mother.

Pediatric Use

Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

CARDURA has been administered to approximately 4000 patients, of whom 1679 were included in the clinical development program. In that program, minor adverse effects were frequent, but led to discontinuation of treatment in only 7% of patients. In placebo-controlled studies adverse effects occurred in 49% and 40% of patients in the doxazosin and placebo groups, respectively, and led to discontinuation in 2% of patients in each group. The major reasons for discontinuation were postural effects (2%), edema, malaise/fatigue, and some heart rate disturbance, each about 0.7%.

In controlled clinical trials directly comparing CARDURA to placebo there was no significant difference in the incidence of side effects, except for dizziness (including postural), weight gain, somnolence and fatigue/malaise. Postural effects and edema appeared to be dose related.

The prevalence rates presented below are based on combined data from placebo-controlled studies involving once daily administration of doxazosin at doses ranging from 1-16 mg. Table 1 summarizes those adverse experiences (possibly/probably related) reported for patients in these studies where the prevalence rate in the doxazosin group was at least 0.5% or where the reaction is of particular interest.

TABLE 1
ADVERSE REACTIONS DURING PLACEBO CONTROLLED STUDIES

		DOXAZOSIN (N=339)	PLACEBO (N=336)
CARDIOVASCULAR:	Dizziness	19%	9%
	Vertigo	2%	1%
	Postural Hypotension	0.3%	0%
	Edema	4%	3%
	Palpitation	2%	3%
	Arrhythmia	1%	0%
	Hypotension	1%	0%
	Tachycardia	0.3%	1%
	Peripheral Ischemia	0.3%	0%
SKIN APPENDAGES:	Rash	1%	1%
	Pruritus	1%	1%
MUSCULOSKELETAL:	Arthralgia/Arthritis	1%	0%
	Muscle Weakness	1%	0%
	Myalgia	1%	0%
CENTRAL & PERIPHERAL N.S.:	Headache	14%	16%
	Paresthesia	1%	1%
	Kinetic Disorders	1%	0%
	Ataxia	1%	0%
	Hypertonia	1%	0%
	Muscle Cramps	1%	0%
AUTONOMIC:	Mouth Dry	2%	2%
	Flushing	1%	0%
SPECIAL SENSES:	Vision Abnormal	2%	1%
	Conjunctivitis/Eye Pain	1%	1%
	Tinnitus	1%	0.3%
PSYCHIATRIC:	Somnolence	5%	1%
	Nervousness	2%	2%
	Depression	1%	1%
	Insomnia	1%	1%
	Sexual Dysfunction	2%	1%
GASTROINTESTINAL:	Nausea	3%	4%
	Diarrhea	2%	3%
	Constipation	1%	1%
	Dyspepsia	1%	1%
	Flatulence	1%	1%
	Abdominal Pain	0%	2%
	Vomiting	0%	1%
RESPIRATORY:	Rhinitis	3%	1%
	Dyspnea	1%	1%
	Epistaxis	1%	0%
URINARY:	Polyuria	2%	0%
	Urinary Incontinence	1%	0%
	Micturation Frequency	0%	2%
GENERAL:	Fatigue/Malaise	12%	6%
	Chest Pain	2%	2%
	Asthenia	1%	1%
	Face Edema	1%	0%
	Pain	2%	2%

Additional adverse reactions have been reported, but these are, in general, not distinguishable from symptoms that might have occurred in the absence of exposure to doxazosin. The following adverse reactions occurred with a frequency of between 0.5% and 1%: syncope, hypoesthesia, increased sweating, agitation, increased weight. The following additional adverse reactions were reported by <0.5% of 3960 patients who received doxazosin in controlled or open, short- or long-term clinical studies, including international studies. *Cardiovascular System:* angina pectoris, myocardial infarction, cerebrovascular accident; *Autonomic Nervous System:* pallor; *Metabolic:* thirst, gout, hypokalemia; *Hematopoietic:* lymphadenopathy, purpura; *Reproductive System:* breast pain; *Skin Disorders:* alopecia, dry skin, eczema; *Central Nervous System:* paresis, tremor, twitching, confusion, migraine, impaired concentration; *Psychiatric:* paroniria, amnesia, emotional lability, abnormal thinking, depersonalization; *Special Senses:* parosmia, earache, taste perversion, photophobia, abnormal lacrimation; *Gastrointestinal System:* increased appetite, anorexia, fecal incontinence, gastroenteritis; *Respiratory System:* bronchospasm, sinusitis, coughing, pharyngitis; *Urinary System:* renal calculus; *General Body System:* hot flushes, back pain, infection, fever/rigors, decreased weight, influenza-like symptoms.

CARDURA has not been associated with any clinically significant changes in routine biochemical tests. No clinically relevant adverse effects were noted on serum potassium, serum glucose, uric acid, blood urea nitrogen, creatinine or liver function tests. CARDURA has been associated with decreases in white blood cell counts (See Precautions).

OVERDOSAGE

No data are available in regard to overdosage in humans.

The oral LD_{50} of doxazosin is greater than 1000 mg/kg in mice and rats. The most likely manifestation of overdosage would be hypotension, for which the usual treatment would be intravenous infusion of fluid. As doxazosin is highly protein bound, dialysis would not be indicated.

DOSAGE AND ADMINISTRATION

DOSAGE MUST BE INDIVIDUALIZED. The initial dosage of CARDURA in hypertensive patients is 1 mg given once daily. This starting dose is intended to minimize the frequency of postural hypotension and first dose syncope associated with CARDURA. Postural effects are most likely to occur between 2 and 6 hours after a dose. Therefore blood pressure measurements should be taken during this time period after the first dose and with each increase in dose. Depending on the individual patient's standing blood pressure response (based on measurements taken at 2-6 hours postdose and 24 hours postdose), dosage may then be increased to 2 mg and thereafter if necessary to 4 mg, 8 mg and 16 mg to achieve the desired reduction in blood pressure. **Increases in dose beyond 4 mg increase the likelihood of excessive postural effects including syncope, postural dizziness/vertigo, postural hypotension. At a titrated dose of 16 mg once daily the frequency of postural effects is about 12% compared to 3% for placebo.**

HOW SUPPLIED

CARDURA (doxazosin mesylate) is available as colored tablets for oral administration. Each tablet contains doxazosin mesylate equivalent to 1 mg (white), 2 mg (yellow), 4 mg (orange) or 8 mg (green) of the active constituent, doxazosin.

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Recommended Storage: Store below 86°F(30°C).

CAUTION: Federal law prohibits dispensing without prescription.

65-4538-00-0 Issued Nov 1990

Pfizer Roerig

Reappraisal by Transesophageal Echocardiography of the Significance of Left Atrial Thrombi in the Prediction of Systemic Arterial Embolization in Rheumatic Mitral Valve Disease

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Systemic arterial embolization imparts a significant risk of serious complications throughout the lives of patients with rheumatic heart disease. Left atrial (LA) thrombi have been thought to be the major source of emboli. A transesophageal echocardiography (TEE) study of 260 consecutive patients with rheumatic mitral valve disease was performed during a period of 24 months, with particular reference to understanding the association between LA thrombi and embolic complications. Of these patients, 155 had predominant mitral stenosis, 24 had significant mitral regurgitation, and the remaining 81 with xenograft mitral valve replacement developed valvular dysfunction (25 resulted in predominant mitral stenosis and 56 in significant mitral regurgitation). LA thrombi were detected in 38 patients (group A) and absent in 222 (group B). Group A patients had a higher frequency of recent (≤1 week before TEE study) and remote (>1 week before) embolization than did group B patients (recent: 26.3 vs 5.4% [p <0.001]; remote: 18.4 vs 5.0% [p <0.01]). The frequency of atrial fibrillation was also greater in group A patients (100 vs 74.3%; p <0.001). The exclusion of patients with significant mitral regurgitation and sinus rhythm had no effect on the association between LA thrombi and evidence of previous embolization. It is concluded that TEE is a convenient diagnostic modality that can be used to identify a subset of patients with rheumatic mitral valve disease at high risk for systemic embolization. Consequently, preventive anticoagulation for possible embolic complications should be more vigorously adhered to in patients with rheumatic mitral valve disease and LA thrombi.

(Am J Cardiol 1992;70:769–773)

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Systemic arterial embolization is a frequent and sometimes catastrophic complication in patients with rheumatic heart disease.[1–4] Some investigators have proposed that most arterial emboli are due to intracardiac mural thrombi.[5–9] Thrombi in the left atrium (the most frequent location) are found in 16 to 64% of patients with rheumatic heart disease in surgical and autopsy studies.[5–8] The correlation between the presence of left atrial (LA) thrombi and the occurrence of systemic arterial embolization was initially suggested by surgery or autopsy studies.[5–7] More recently, 2-dimensional transthoracic echocardiography has also supported this correlation.[9] Although this modality has the advantage of being noninvasive, there are well-recognized limitations in detecting LA thrombi, especially those in the LA appendage.[10–14] Transesophageal echocardiography (TEE) was recently shown to be highly sensitive for detecting LA thrombi (including the LA appendage) compared with direct visualization at the time of surgery.[15,16] Therefore, in this study we used TEE to evaluate the association between LA thrombi and systemic arterial embolization in patients with rheumatic mitral valve disease.

METHODS

Study patients: Consecutive patients with rheumatic mitral valve disease referred to the echocardiography laboratory at the National Taiwan University Hospital from January 1989 to December 1990 were enrolled in this study. The diagnosis of rheumatic valvular disease was based on clinical, electrocardiographic, radiologic and echocardiographic examinations. Patients who had undergone xenograft mitral valve replacement for rheumatic heart disease and developed xenograft dysfunction were also included. Patients with infective endocarditis, mechanical valve replacements or other causes of valvular dysfunction were excluded. All patients underwent hemodynamic and angiographic studies.

In all, there were 260 patients (105 men and 155 women, age range 18 to 75 years, mean 45 ± 13). Patients were categorized as having significant mitral regurgitation if they had (by angiography) grade III or IV mitral regurgitation using Sellers' criteria, regardless of mitral valve area. Patients with mitral valve area <1.5 cm^2 and no significant mitral regurgitation were categorized as having predominant mitral stenosis. Of

TABLE I Comparisons of Recent, Remote and Total Systemic Arterial Embolization, and Atrial Fibrillation Between Patients With (group A) and Without (group B) Left Atrial Thrombi

	No. of Pts.	Systemic Arterial Embolization			Atrial Fibrillation
		Recent	Remote	Total	
Group A	38	10 (26.3%)*	7 (18.4%)†	17 (44.7%)*	38 (100%)*
MS	30	7 (23.3%)‡	6 (20%)†	13 (43.3%)*	30 (100%)*
XGT (MS)	8	3 (37.5%)*	1 (12.5%)	4 (50%)†	8 (100%)
Group B	222	12 (5.4%)	11 (5%)	23 (10.4%)	165 (74.3%)
MS	125	10 (8%)	7 (5.6%)	17 (13.6%)	80 (64%)
MR	24	2 (8.3%)	0 (0%)	2 (8.3%)	18 (75%)
XGT (MS)	17	0 (0%)	1 (5.9%)	1 (5.9%)	16 (94.1%)
XGT (MR)	56	0 (0%)	3 (5.4%)	3 (5.4%)	51 (91.1%)

*$p < 0.001$; †$p < 0.01$; ‡$p < 0.05$ (comparisons between groups A and B and subgroups in native valve or post-xenograft replacement with or without left atrial thrombi.
MR = mitral regurgitation; MS = mitral stenosis; XGT = xenograft dysfunction.

TABLE II Sites of Lodgment of 48 Emboli Occurring in 40 Patients

Site	Number (%)
Brain	34 (71)
Kidney	3 (6)
Mesenteric arteries	4 (8)
Lower extremities	7 (15)

179 patients with native valves, 155 had predominant mitral stenosis and 24 had significant mitral regurgitation. The remaining 81 patients had previously undergone xenograft mitral valve replacement, and 25 of these had developed predominant mitral stenosis and 56 significant mitral regurgitation. Only 10 patients were receiving oral anticoagulant treatment with warfarin before referral to our laboratory.

Transthoracic echocardiography: Transthoracic echocardiography was performed using a 2.5 or 3.75 MHz phased-array transducer connected to an ultrasound imaging system (Toshiba SSH-65A). Both routine M-mode and 2-dimensional echocardiographic studies were performed in all patients, and measurements were interpreted according to the standards of the American Society of Echocardiography.[17] Mitral valve area was determined using the Doppler pressure half-time method and averaged over 5 consecutive beats.[18]

Transesophageal echocardiography: TEE was performed using a 3.75 MHz transducer attached to the tip of a commercially available gastroscope and connected to a Toshiba SSH-65A real-time phased-array sector scanner. All patients fasted for ≥4 hours before the examination, and a topical oropharyngeal lidocaine spray was applied immediately before insertion of the gastroscope. With the patient lying in the left lateral position and monitored by means of a 3-lead electrocardiogram, the gastroscope was advanced into the esophagus. From the esophageal short-axis view, the left atrium could be scanned without hindrance from anatomic obstacles. With a 20° counterclockwise rotation of the gastroscope at the level of the aortic valve, the LA appendage could be seen as an outward pouch in the anterolateral region of the atrial cavity. The study was usually completed within 10 minutes and was generally well-tolerated.

Left atrial thrombus: The presence of LA thrombus was established by demonstrating a well-circumscribed echogenic mass with echotexture different from that of the atrial wall, despite alterations in gain settings. All examinations were recorded on videotape and reviewed by 2 echocardiographers. The examiners were unaware of patients' embolic history.

Systemic arterial embolization: In addition to chart review, detailed historical information was elicited by physicians using a question list specifically aimed at detecting embolic events. Clinical diagnosis of an embolic transient ischemic attack or stroke was obtained by neurologists. This diagnosis included patients experiencing the abrupt onset of a focal neurologic deficit in the vascular territory of the anterior or middle cerebral arteries, with no evidence of mass or hemorrhage on head computed tomography scan. Patients with deficits in the territory of the posterior circulation or lacunar strokes were excluded.

Angiography was used to confirm the diagnosis of peripheral emboli involving the kidneys, mesenteric arteries or extremities. Patients with vague symptoms suggestive of peripheral embolization without angiographic proof were excluded.

Embolic phenomena were classified as recent embolization if they occurred ≤1 week before TEE and as remote embolization if they occurred >1 week before.

Statistical analysis: The chi-square and Fisher's exact tests were used to correlate LA thrombosis with systemic arterial embolization. A p value <0.05 was considered statistically significant.

RESULTS

Left atrial thrombi: LA thrombi were present (group A) in 38 of 260 patients (15%) and absent (group B) in 222 (Table I). Thrombi were absent in all patients with significant mitral regurgitation. Therefore, excluding patients with significant mitral regurgitation, the frequency of LA thrombi among patients with predominant mitral stenosis was 21% (38 of 180). Only 21 pa-

tients (55%) in group A were found to have LA thrombi by transthoracic echocardiography, and most missed cases had LA thrombi located in the LA appendage (1 in LA cavity, and 16 in LA appendage).

Frequency of systemic embolic events: Evidence of systemic embolization was present in 40 patients (15%) who had a total of 48 embolic episodes (Tables I and II). Twenty-two patients had embolic phenomena occurring ≤1 week before TEE and were categorized as recent embolization. The remaining 18 patients had only remote embolic events.

Most emboli involved the central nervous system (71%), and the remainder involved the kidneys, mesenteric arteries and lower extremities (Table II). Transient ischemic attack was present in 7 patients (2 in group A, and 5 in group B).

Influence of anticoagulation: Of 10 patients studied while receiving long-term anticoagulant therapy, 2 showed the presence of LA thrombi (20%). There was no significant difference between patients with and without anticoagulant treatment with regard to presence or absence of LA thrombi (p = 0.28). All patients had been treated with anticoagulant therapy after they experienced embolic events, and recurrent embolic episodes occurred in 1 while receiving warfarin treatment.

Atrial fibrillation: There were 203 patients (78.1%) with atrial fibrillation in this study (Table I). All patients in group A had atrial fibrillation, and the frequency was higher than that in group B (100 vs 74.3%; p <0.001). All except 2 patients with evidence of systemic embolization had chronic atrial fibrillation.

Correlation between left atrial thrombi and systemic arterial embolization: Evidence of previous embolization was more frequent in group A than in B (44.7 vs 10.4%; p <0.001) (Figure 1). Recent or remote embolization was also more frequent in group A (recent: 26.3 vs 5.4% [p <0.001]; remote: 18.4 vs 5.0% [p <0.01]). A similar correlation was found in subgroups with native valves or xenografts. The exclusion of patients with significant mitral regurgitation and sinus rhythm had no

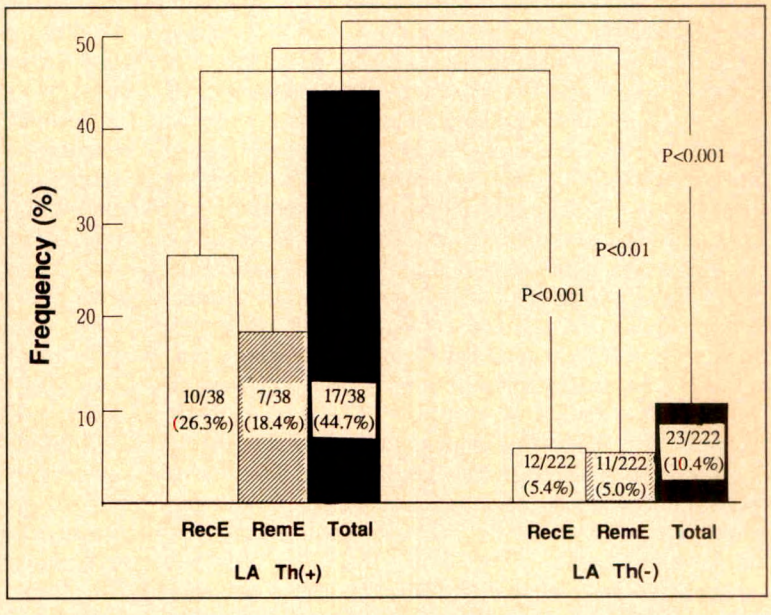


FIGURE 1. Frequency of recent embolization (RecE) and remote embolization (RemE), and history of embolization (Total) in 260 patients with (+) or without (−) left atrial thrombi (LA Th).

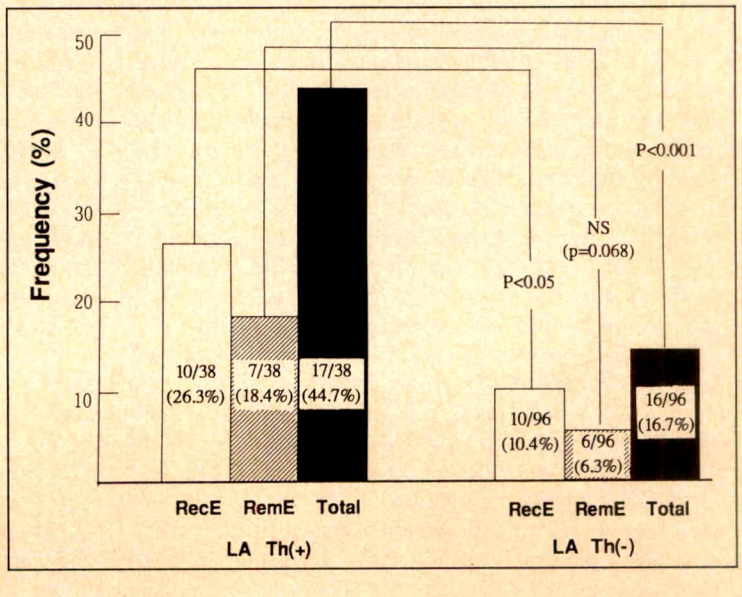


FIGURE 2. Frequency of recent embolization (RecE) and remote embolization (RemE), and history of embolization (Total) in 134 patients with (+) or without (−) left atrial thrombi (LA Th), excluding those with significant mitral regurgitation and sinus rhythm. NS = not significant.

TABLE III Systemic Arterial Embolization in Different Sites of Left Atrial Thrombi

Site	History of Embolization	No Embolization
Left atrial cavity (n = 16)	8 (50%)	8 (50%)
Left atrial appendage (n = 17)	7 (41%)	10 (59%)
Both sites (n = 5)	2 (40%)	3 (60%)

Comparisons between subgroups are statistically insignificant.

effect on this association, except for the frequency of remote embolization, which approached statistical significance ($p = 0.068$) (Figure 2).

Location of left atrial thrombi and systemic arterial embolization: Of 38 LA thrombi, 16 were in the LA main cavity (42%), 17 in the LA appendage (45%) and 5 in both sites (13%) (Table III). The frequency of systemic embolization was unrelated to the location of LA thrombi.

DISCUSSION

In Taiwan, rheumatic heart disease remains a frequent cause of cardiac morbidity and mortality, although the incidence is decreasing.[9] In these patients, systemic arterial embolization is a serious and sometimes fatal complication.[1–4] According to the report by Jordan et al,[5] Willus published the first report on embolic manifestations of heart disease in 1926. In 1933, Weiss and Davis[1] found evidence of embolism at autopsy in 45% of 164 patients with rheumatic heart disease. Several studies have since confirmed that rheumatic heart disease is frequently associated with systemic embolization. Intracardiac thrombi have been suggested to be the major source of emboli.[5–9] TEE was recently shown to be a method of detecting LA thrombi reliably in living patients.[15,16] In this study, we examined the relation between LA thrombi detected by TEE and systemic arterial embolization in patients with rheumatic mitral valve disease.

Systemic arterial embolization: We found evidence of embolization in 15% of patients. This is consistent with previous studies that found systemic embolization in 10 to 45% of patients with rheumatic mitral valve disease.[1–4] Autopsy studies generally report a higher frequency, most likely because they can demonstrate subclinical infarcts. For the same reason, there is a considerable discrepancy between clinical and autopsy studies in the locations of embolization. Whereas cerebral emboli are usually overt, visceral emboli more often occur without patients' knowledge. This may explain the high frequency of cerebral emboli in this clinical study (71%) compared with that in autopsy series.[5–8]

The prognosis of systemic embolization is sometimes grave.[19,20] Approximately one sixth to one third of patients do not survive the first cerebral embolism, and one third of survivors die in ≤1 year, mostly because of recurrent embolism. Delay in the management of emboli to the extremities may lead to amputation of the affected limb. Clearly, systemic embolization is a constant and undesirable threat in patients with rheumatic heart disease.

Left atrial thrombi: We detected LA thrombi in 15% of patients with rheumatic mitral valve disease and in 21% of those with predominant mitral stenosis. In previous studies, intracardiac mural thrombi were found in 16 to 64% of patents with rheumatic heart disease.[5–9,20] Most of these thrombi are located in the left atrium, and mural thrombi seldom occur in the ventricles or right atrium.[5]

Earlier studies were limited to surgical or autopsy detection of intracardiac thrombi.[5–8] More recently, levophase pulmonary arteriography,[21,22] coronary angiography,[23,24] M-mode and 2-dimensional echocardiography[10–14] and computed tomography[25] were used with variable sensitivity and specificity. Because of technical limitations, 2-dimensional transthoracic echocardiography is relatively insensitive for detecting LA thrombi, although it has the advantage of being noninvasive.[10–14] TEE provides detailed images of the left atrium (especially the LA appendage) and is unhindered by anatomic obstacles. It was recently shown to be the most sensitive method for detecting LA thrombi.[15,16] The advent of TEE has enabled us to study patients who do not need surgery and perhaps at an earlier stage in their diseases.

Correlation between left atrial thrombi and systemic arterial embolization: Previous studies concerning the relation between intracardiac thrombi and systemic arterial embolization were based on surgery, autopsy or transthoracic echocardiography.[6–9] These studies were likely biased, because they only included selected patients or were based on a less sensitive modality. Our results confirmed a higher frequency of both atrial fibrillation and systemic arterial embolization among patients with LA thrombi in a large group of unselected patients with rheumatic mitral valve disease.

Previous reports did not differentiate between recent and remote embolic manifestations. This differentiation may be important, because LA thrombi may have formed after embolism occurred,[6–9] or thrombi that were present at the time of embolism may have resolved with anticoagulant therapy.[26–28] We showed that the association between LA thrombi and systemic embolization was not dependent on the timing of embolic events. We also showed that the location of the thrombi within the left atrium had no effect on the frequency of systemic arterial embolization.

Study limitations: We included only patients with rheumatic mitral valve disease affecting native valves or xenografts. LA thrombi may occur in other conditions such as atherosclerotic heart disease with atrial fibrillation, cardiomyopathy or in patients with mechanical valve replacements. We do not know whether the present findings can be applied to those conditions.

Furthermore, other conditions such as LA spontaneous echo contrast, atrial septal aneurysm, patent foramen ovale, mitral valve prolapse and left ventricular hypokinesia with or without thrombi have been reported to predispose patients to systemic embolization.[29,30] Recently, the degree of LA mechanical dysfunction was suggested to have a role in the pathogenesis of LA clot formation, and LA appendage contractile function was studied with pulsed Doppler imaging of flow in the ap-

pendage.[31] There may be some limitations to this study, because we did not examine the contribution of these factors to the frequency of embolism.

Moreover, the age of thrombus is difficult to determine by echocardiography, even with the aid of TEE, and the emboli may be from the fresh thrombi or the blood clot overlying the organized thrombi.[9] Thus, we did not attempt to include this variable in the analysis.

Finally, it is possible that many patients with recent embolic events may have been referred for TEE to rule out cardiac sources of emboli, although this potential referral bias was minimized by using consecutive patients as the study population.

Clinical implication: TEE is a convenient and accurate means of detecting LA thrombi, especially those located in the LA appendage. It enabled us to confirm the association between LA thrombi and systemic embolization in a large group of unselected patients with rheumatic mitral valve disease, which would have been difficult in previous years using less sensitive methods or even surgery or autopsy. Patients with rheumatic heart disease have a constant risk of systemic embolization, and anticoagulant therapy is recommended in those with atrial fibrillation or history of embolization if not contraindicated.[32,33] We found that patients with LA thrombi have a significantly higher risk for systemic embolization, especially those with predominant mitral stenosis and atrial fibrillation. Based on our findings, preventive anticoagulation should be more vigorously adhered to in these patients.

Acknowledgment: We wish to express our cordial thanks to Joe Cohen, MD, for revising the manuscript, and to Hwei-Ming Kuo and Huey-Yann Chang for collecting data. We are also grateful to Mei-Huei Feng for continuing assistance in the echocardiography laboratory.

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Usefulness of Left Atrial and Left Ventricular Chamber Sizes as Predictors of the Severity of Mitral Regurgitation

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Left ventricular (LV) and left atrial (LA) chamber sizes are frequently used to assist in assessing the severity of mitral regurgitation (MR). To study the reliability of these measurements in the clinical setting 2-dimensional echocardiographic measurements of the left ventricle and left atrium were obtained in 92 consecutive patients with MR present on both angiography and Doppler echocardiographic examinations performed within 2.8 ± 2.5 days of each other. The accuracy of chamber dimensions in identifying severe MR (angiographic grade 3 to 4+) was determined in the total population and the following patient subgroups: (1) isolated chronic MR with preserved LV function inclusive of all rhythms; (2) isolated chronic MR, preserved LV function and sinus rhythm; (3) isolated chronic MR with LV dysfunction; (4) chronic MR associated with other valvular disease; and (5) acute MR. Only in subgroup 2 were chamber sizes reliable in identifying severe MR. Atrial dimensions provided the most accurate assessment with an LA volume >58 ml, anteroposterior dimension >45 mm and superoinferior dimension >55 mm, with sensitivities of 75, 75 and 88%, specificities of 83, 100 and 83%, positive predictive values of 92, 100, and 93% and negative predictive values of 56, 60, and 71%, respectively. LV dimensions had excellent positive predictive values but lower sensitivities. Normalizing for body surface area did not improve the accuracy of uncorrected dimensions. Although increased LA and LV dimensions can identify severe MR, smaller dimensions do not exclude this diagnosis. With acute MR, atrial fibrillation, LV dysfunction or associated valvular disease, these dimensions are not reliable.

(Am J Cardiol 1992;70:774–779)

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The management of patients with mitral regurgitation (MR) depends largely on the severity of regurgitation and on left ventricular (LV) systolic function.[1,2] Echocardiography has enabled accurate assessment of LV function; however, simple noninvasive quantitation of MR has been elusive despite advances in color flow Doppler technology. This relates to the dependence of color Doppler regurgitant jet areas not only on the regurgitant volume but also on physical factors such as driving pressure, flow rate, orifice size and jet orientation, as well as on technical factors such as instrument gain, pulse repetition frequency and transducer frequency.[3–6] Thus, in addition to Doppler assessment, left atrial (LA) and LV chamber sizes are frequently relied on to assist in the quantitation of MR severity in diverse clinical settings given the assumption that chronic volume overload will lead to progressive chamber dilation. There is a paucity of evidence validating this approach. This study was designed to examine the accuracy of commonly used 2-dimensional echocardiographic LA and LV chamber dimensions in identifying severe MR.

METHODS

Patients: The study population was retrospectively identified over a 28-month period between January 1988 and April 1991, and consisted of 92 consecutive patients with MR present on both cardiac catheterization and echocardiography performed within 2 weeks of each other. Patients with prosthetic valves in any position were excluded.

Echocardiography: All patients underwent complete echocardiographic studies (ATL Ultramark 9, Ultramark 8 and Mark 600 echocardiographic systems). MR was diagnosed when conventional pulsed or color flow Doppler examination demonstrated the presence of a systolic signal in the left atrium that extended for more than one half of systole and could be detected beyond the immediate coaptation point of the mitral leaflets.[7,8] Measurements of intracardiac dimensions were made from the videotape images, averaged from a minimum of 3 cardiac cycles, with the assistance of an Apple 2E off-line analysis station and Digisonics software program.

LA dimensions (Figure 1) were measured at end-systole, 1 frame prior to mitral valve opening. LA anteroposterior dimensions were obtained from the parasternal long-axis view, measured from the leading edge of the posterior aortic root to the leading edge of the posterior LA wall at the level of the aortic cusps, similar to the American Society of Echocardiography recommen-

dations for M-mode LA dimensions.[9] From the apical 4-chamber view, LA superoinferior dimensions were measured from the midpoint of the line joining the 2 attachment points of the mitral leaflets to the annulus, to the leading edge of the atrial superior border. LA mediolateral dimensions were measured from the interatrial septum to the lateral boundary of the atrium at its maximum dimension. Care was taken not to include the pulmonary veins in these measurements. Using the 3 orthogonal dimensions, LA volume was calculated assuming that the chamber cavity resembled a prolate ellipse.[10]

The LV anteroposterior diameter was obtained from the left parasternal long-axis view at the onset of the QRS deflection and at end-systole (Figure 1). Measurements were made from the interventricular septum to the leading edge of the posterior wall at the level of the chordal-mitral leaflet junction. Fractional shortening was calculated as the difference between end-diastolic and end-systolic dimensions divided by the end-diastolic dimension. LV mediolateral dimensions were obtained from the apical 4-chamber view, from the interventricular septum to the lateral ventricular border at the chordal-mitral leaflet junction.

Individual atrial and ventricular dimensions were normalized for body surface area. Atrial dimensions were also indexed to aortic root diameter and right atrial width (Figure 1) by calculating the ratio of the LA anteroposterior and aortic root dimensions, and the LA and right atrial mediolateral dimensions.

Catheterization: All patients had single-plane (30° right anterior oblique) or biplane (30° right anterior and 60° left anterior oblique) ventriculograms that allowed calculation of ejection fraction and MR quantitation. Regurgitation severity was graded from +1 to +4 based on standard Sellers' criteria.[11] LA pressure was directly measured where transseptal procedures were performed or estimated using the pulmonary capillary wedge pressure obtained during right-heart catheterization with fluid-filled catheters.

Data analysis: Direct measurements of left heart chamber dimensions, those corrected for body surface area, and those indexed to other cardiac dimensions were evaluated for their accuracy in differentiating severe (3 to 4+) from mild-moderate (1 to 2+) MR in the total population and various patient subgroups: (1) isolated chronic MR with preserved LV function (inclusive of atrial fibrillation); (2) isolated chronic MR, preserved LV function and sinus rhythm; (3) isolated chronic MR with LV dysfunction; (4) chronic MR associated with valvular disease of moderate or severe degree; and (5) acute MR.

Chronic MR was defined as MR which was at least 1 month from onset based on symptoms or previous documentation of regurgitation. Acute MR included patients with <1 month history of MR. Patients with MR discovered incidentally and believed unrelated to their current illness were classified as chronic MR. LV dysfunction was defined by echocardiographic examination as a fractional shortening <25%.

In each subgroup, breakpoints for each cardiac dimension were identified that diagnosed ≥75% of patients with severe MR with a specificity of ≥80%. In a population with an intermediate probability of severe MR (50%), Bayes' theorem would predict the positive predictive value for severe regurgitation to be 80% if the chamber size provided a sensitivity and specificity of 75% and 80%, respectively. Higher sensitivities or specificities result in an increase in the positive predictive value. Lower values would provide positive predictive values that are <80% and unlikely to be clinically useful.

Statistical analysis: Values are expressed as mean dimension ±1 standard deviation. Group mean differences were assessed by Student's *t* test. Sensitivity was defined as TP/(TP + FN), specificity as TN/(FP + TN), positive predictive value as TP/(TP + FP), and negative predictive value as TN/(TN + FN), where TP is true-positive identification, FP false-positive identification, TN true-negative identification, and FN false-negative identification. Within each subgroup, Pearson's chi-square or Fisher's exact test was used to compare the relative frequency of chamber sizes larger and smaller than the identified dimensions in patients with mild-moderate and severe MR. All p values were 2-sided; p values ≤0.05 were considered significant.

RESULTS

Study patients: Over the 28-month period, 92 patients had both a technically adequate echocardiographic and angiographic examination demonstrating MR and were free of valve prostheses. The mean duration between studies was 2.8 ± 2.5 days. Severe regurgitation was present in 45 patients (mean age 63 ± 14 years) and mild-moderate regurgitation in 47 patients (mean age 62 ± 15 years). Only 6 patients had acute

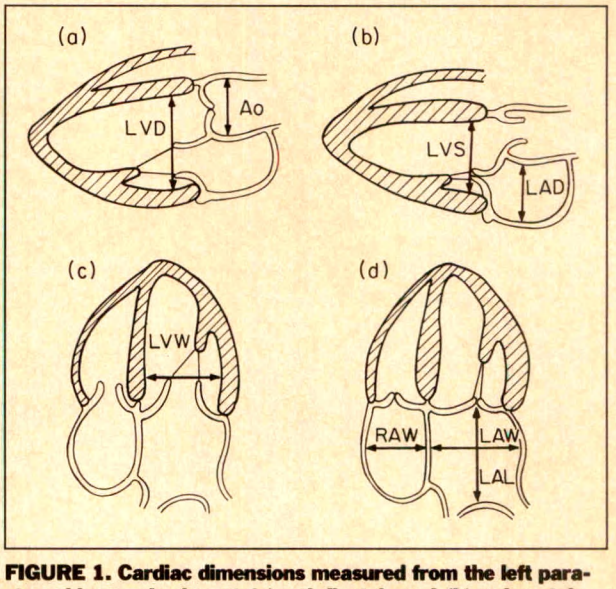


FIGURE 1. Cardiac dimensions measured from the left parasternal long-axis view at *(a)* end-diastole and *(b)* end-systole; the apical 4-chamber view at *(c)* end-diastole and *(d)* end-systole. Ao = aortic root diameter; LAD = anteroposterior left atrial dimension; LAL = superoinferior left atrial dimension; LAW = mediolateral left atrial dimension; LVD = anteroposterior left ventricular diastolic dimension; LVS = anteroposterior left ventricular systolic dimension; LVW = mediolateral left ventricular diastolic dimension; RAW = mediolateral right atrial width.

TABLE I Cardiac Dimensions in the Total Population (n = 92) with Mitral Regurgitation

Dimensions	Mild-Moderate MR (n = 47)	Severe MR (n = 45)	p Value
LA volume (ml)	69 ± 48	104 ± 61	0.004
LA anteroposterior (mm)	46 ± 9	51 ± 9	0.01
LA superoinferior (mm)	57 ± 10	65 ± 12	0.001
LA mediolateral (mm)	47 ± 9	55 ± 13	<0.001
LV anteroposterior (mm)	53 ± 9	55 ± 8	NS
LV mediolateral (mm)	47 ± 7	50 ± 7	NS
Fractional shortening (%)	23 ± 10	30 ± 11	0.002
Ejection fraction (%)	45 ± 18	56 ± 17	0.002

LA = left atrial; LV = left ventricular; MR = mitral regurgitation; NS = not significant.

MR, whereas 86 patients had chronic MR. Isolated MR was present in 68 patients while 24 patients had associated valvular heart disease of moderate or severe degree (13 with aortic stenosis, 3 with aortic insufficiency, 7 with mitral stenosis, and 1 with atrial septal defect). Preserved LV function was present in 49 patients with the remaining 43 patients having LV dysfunction.

Dimensions in the total population with mitral regurgitation: Patients with severe MR generally had greater LA dimensions than patients with mild-moderate MR (Table I). LV dimensions were not significantly different among the 2 degrees of regurgitation. However, the fractional shortening and angiographic ejection fraction were larger when severe MR was present. Despite the differences in mean atrial dimensions, significant overlaps were present such that no single dimension provided good sensitivity, specificity or positive predictive value for severe regurgitation (Figure 2).

Isolated chronic mitral regurgitation with preserved left ventricular function: Of the 29 patients with chronic MR with no other valvular abnormalities and a fractional shortening ≥25%, regurgitation was severe in 20 patients and mild-moderate in 9 patients. LA anteroposterior dimension >45 mm, superoinferior dimension >55 mm and volume >58 ml provided the best discriminator of severe MR, although no dimension identified 75% of patients with severe MR and yet maintained a specificity of 80% (Table II). LV dimensions did not achieve equal sensitivity without markedly compromising specificity and positive predictive value.

When patients with atrial fibrillation were excluded from this population, severe regurgitation was better discriminated in the remaining 22 patients (Table II). LA volume >58 ml identified 75% of severe MR with a specificity of 83% and positive predictive value of 92%. LA anteroposterior dimension >45 mm identified 75% of patients with severe regurgitation and had a specificity and positive predictive value of 100%. LA superoinferior dimension >55 mm correctly identified 88% of patients with severe MR with a specificity of 83% and positive predictive value of 93%. Indexing LA dimen-

TABLE II Sensitivity, Specificity and Predictive Values of Cardiac Dimensions for Severe Mitral Regurgitation (MR) in 22 Patients with Isolated Chronic MR, Preserved Left Ventricular (LV) Function and Sinus Rhythm (and the 29 patients with isolated chronic MR and preserved LV function inclusive of all rhythms)

Dimensions	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	p Value
LA volume >58 ml	75 (80)	83 (67)	92 (84)	56 (60)	0.02 (0.03)
LA volume >33 ml/m^2	73 (79)	83 (67)	92 (83)	56 (60)	0.05 (0.03)
LA anteroposterior >45 mm	75 (80)	100 (67)	100 (84)	60 (60)	0.003 (0.03)
LA superoinferior >55 mm	88 (85)	83 (56)	93 (81)	71 (63)	0.004 (NS)
LA mediolateral >50 mm	63 (65)	83 (67)	91 (81)	45 (46)	NS (NS)
LV anteroposterior >56 mm	44 (40)	83 (78)	88 (80)	36 (37)	NS (NS)
LV mediolateral >50 mm	50 (47)	100 (100)	100 (100)	38 (40)	NS (0.03)
LV anteroposterior >32 mm/m^2	60 (47)	83 (67)	90 (75)	45 (38)	NS (NS)

p values for chi-square analysis.
NPV = negative predictive value; PPV = positive predictive value; other abbreviations as in Table I.

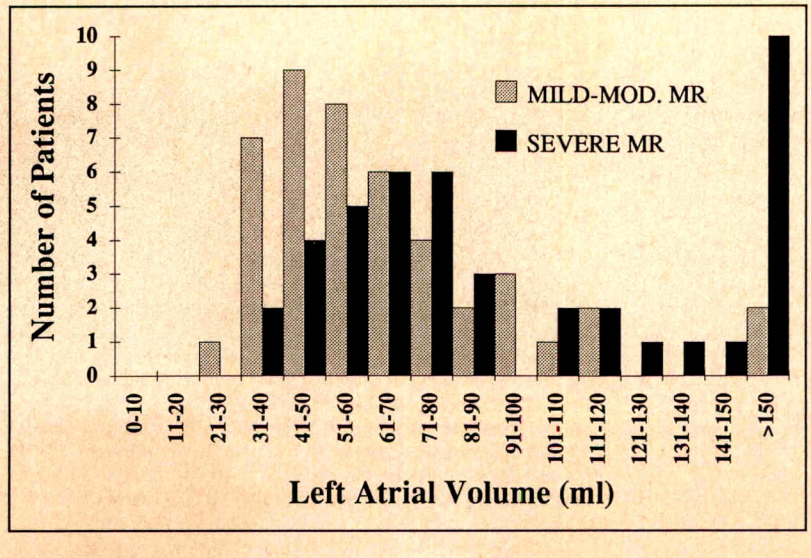


FIGURE 2. Distribution of left atrial volumes in the total population with mitral regurgitation (MR). MOD. = moderate.

TABLE III Sensitivity, Specificity and Predictive Value of Left Atrial Dimensions for Severe Mitral Regurgitation in Subgroups

Subgroup Population	No. of Pts.	Dimension	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	p Value
All patients	92	LA volume >58 ml	84	49	61	76	0.001
		LA anteroposterior >45 mm	67	60	61	65	0.01
		LA superoinferior >55 mm	84	51	62	77	<0.001
Subgroup 1	29	LA volume >58 ml	80	67	84	60	0.03
		LA anteroposterior >45 mm	80	67	84	60	0.03
		LA superoinferior >55 mm	85	56	81	63	NS
Subgroup 2	22	LA volume >58 ml	75	83	92	56	0.02
		LA anteroposterior >45 mm	75	100	100	60	0.003
		LA superoinferior >55 mm	88	83	93	71	0.004
Subgroup 3	33	LA volume >58 ml	80	60	50	86	NS
		LA anteroposterior >45 mm	55	59	40	72	NS
		LA superoinferior >55 mm	70	65	50	81	NS
Subgroup 4	24	LA volume >58 ml	100	33	44	100	NS
		LA anteroposterior >45 mm	67	60	50	75	NS
		LA superoinferior >55 mm	100	33	44	100	NS

p values for chi-square analysis.
Subgroup 1 = isolated chronic mitral regurgitation (MR) with preserved left ventricular (LV) function; Subgroup 2 = isolated chronic MR, preserved LV function and sinus rhythm; Subgroup 3 = isolated chronic MR with LV dysfunction; Subgroup 4 = chronic MR with associated valve disease; other abbreviations as in Tables I and II.

sions for body surface area, right atrial size or aortic root size did not improve sensitivity or specificity. LV dimensions alone had lower sensitivities when achieving equivalent specificities and positive predictive values. Normalizing LV dimensions for body surface area resulted in some improvement in identifying severe MR; however, atrial dimensions were still superior. LV dimensions did not add to the accuracy of atrial indexes when the 2 were combined.

Isolated chronic mitral regurgitation with left ventricular dysfunction: Of the 33 patients with isolated chronic MR and a fractional shortening <25%, 11 patients had severe regurgitation and 22 patients had mild-moderate regurgitation. Mean LA volume was greater in patients with severe MR. Individual atrial dimensions demonstrated a large standard deviation, but tended to be greater when severe regurgitation was present. As with the total population there was substantial overlap of atrial dimensions between the 2 regurgitant degrees to the extent that severe MR was poorly identified. Discriminating ability did not improve when patients with atrial fibrillation were excluded. No atrial dimension or dimension indexed for body surface area or other chamber size provided a sensitivity of 75% and specificity or positive predictive value ≥80% (Table III). Best results were obtained with LA volume >38 ml/m^2, which had a sensitivity of 71%, specificity of 84%, but a poor positive predictive value of 63%. LV dimensions were not significantly different between the 2 degrees of regurgitation.

Chronic mitral regurgitation with associated valvular disease: There was a trend for all LA dimensions to be greater in patients with severe MR, although with the large range of dimensions none were statistically different. Uncorrected LV dimensions were not significantly different; however, the anteroposterior dimension normalized for body surface area was greater with severe regurgitation (29 ± 5 vs 34 ± 6 mm/m^2; p = 0.04). No atrial or ventricular dimension could provide a 75% sensitivity with a specificity ≥80% (Table III).

Acute mitral regurgitation: Of 6 patients with acute regurgitation, 5 were classified as severe. An LA anteroposterior dimension >45 mm identified 2 patients with severe MR; an LA superoinferior dimension >55 mm and LA volume >58 ml each identified only 3 patients.

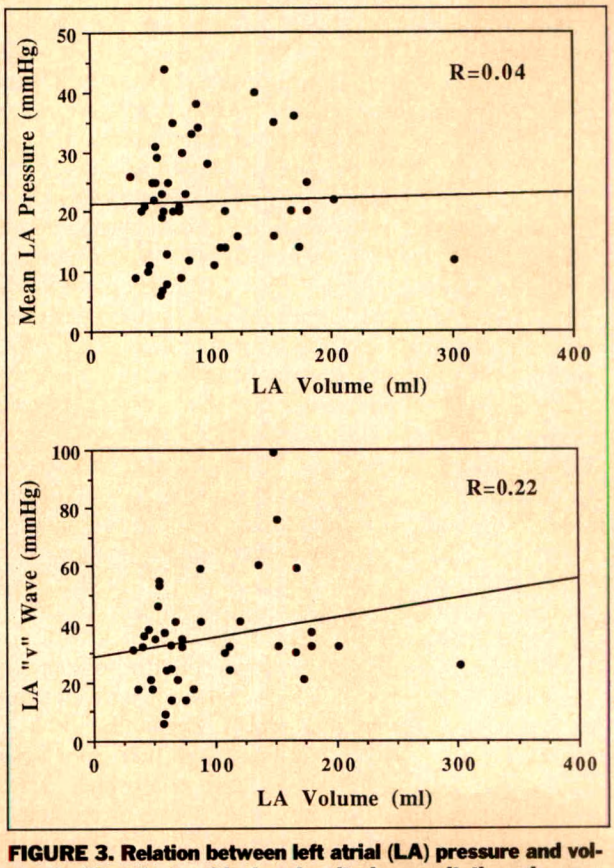


FIGURE 3. Relation between left atrial (LA) pressure and volume in 47 patients with chronic mitral regurgitation who underwent either transseptal or right-heart catheterization.

The 1 patient with mild-moderate MR had LV dysfunction with an LA anteroposterior dimension <45 mm, superoinferior dimension <55 mm but an LA volume of 63 ml.

Left atrial pressure-volume relationship: LA pressures were measured directly by transseptal procedure or indirectly by right-heart catheterization in 47 patients with chronic MR. The correlation of atrial volume with both mean LA pressure ($r = 0.04$) and v wave pressure ($r = 0.22$) was poor (Figure 3).

DISCUSSION

Despite the widespread use of cardiac chamber sizes to assist in quantitating MR severity by Doppler echocardiography, there has been a paucity of evidence validating their usefulness in the diverse clinical settings in which MR occurs. Many conditions modify LA and LV size independent of the presence of MR. Mitral and aortic valve disease, atrial fibrillation, and LV dysfunction are all frequent clinical entities that have been associated with increased atrial size.[1,12–18] Ventricular size is commonly affected by mitral and aortic valve disease, and LV systolic function.[1,19–21] Using chamber sizes in these settings could lead to a false conclusion about regurgitant severity.

Our goal was to identify patient subgroups and cardiac dimensions in which a significant proportion of severe MR would be identified (sensitivity ≥75%) and yet an adequate degree of accuracy (specificity ≥80%) would be maintained. Baysian analysis predicts severe MR in 80% of subjects when these arbitrary "cut off" values are used in a population with an intermediate probability (50%) of severe regurgitation. Higher sensitivity and specificity result in greater positive predictive values, whereas lower values lead to predictive values that are not useful for management decision-making. We found that chamber sizes fulfilled these criteria in only patients with isolated chronic MR with preserved LV function and sinus rhythm. This subgroup represented a fairly small percentage (24%) of the total native valve MR population. Either LA anteroposterior dimension (>45 mm), superoinferior dimension (>55 mm) or LA volume (>58 ml) identified severe MR with a high sensitivity, specificity and positive predictive value. Both atrial and ventricular dimensions have been shown to correlate with body surface area,[12,14,22–24] although other studies have found the correlation with atrial dimensions to be weak or absent.[25,26] Normalizing LA size to body surface area, or to aortic root or right atrial size, did not improve uncorrected measurements in this subgroup. Normalizing dimensions in other subgroups did not improve the sensitivity and specificity to ≥75 and ≥80%, respectively.

LA anteroposterior and superoinferior dimensions are easily acquired with single measurements and thus have technical advantages over LA volume which requires 3 orthogonal dimensions to be measured accurately. The failure of atrial volume to provide a better index of regurgitant severity than single atrial dimensions may relate to several factors. First, measurement of mediolateral dimensions, a component of the volume calculation, are complicated by technical factors that effect lateral resolution, such as the parallel relation of the atrial walls and 2-dimensional ultrasound beam, and beam dispersion in the far field.[27] Second, asymmetric atrial enlargement can occur, and the assumption of a prolate ellipse to represent the atrial cavity may be inadequate in different settings of atrial enlargement.[12,28] Third, a much larger population size may better determine a hierarchy of accuracy among the 3 atrial measurements and could potentially demonstrate an advantage to volume determination.

The accuracy of LV dimensions although improved by normalizing for body surface area was inferior to LA measurements in isolated chronic MR with preserved LV function and sinus rhythm. We hypothesize that this relates to 2 factors. First, the range of normal end-diastolic volumes for the left ventricle (55 ± 10 ml/m^2)[29] is larger than LA end-systolic volumes (20 ± 6 ml/m^2)[26]; thus, a ventricle that initially has low normal dimension may dilate with severe MR, yet still remain within the normal range. The smaller range for atrial volumes makes this less likely to occur. Second, because LV volume is larger than atrial volume, any absolute increase in volume imparted by MR would result in a larger percent change in atrial than ventricular dimensions. Thus, detection of increased volume would be more likely for atrial than ventricular dimensions. This mechanism could be confounded by large volumes of regurgitation that reflux through the atrium into the pulmonary veins.

The population with acute severe regurgitation was small because of the strict criteria used to define this group, but LA enlargement was less frequent. In acute MR, LA and LV dimensions may not provide a reliable diagnosis of severe MR because these chambers do not have time to dilate in response to the increase in volume and pressure.[30]

The presence of LV dysfunction, atrial fibrillation, or associated valvular disease of moderate and/or severe degree was associated with atrial dilation and a resultant deterioration in the sensitivity and specificity of LA dimensions. These conditions are frequently associated with an increase in LV end-diastolic pressure and/or LA pressure and would thus be expected to act as a stimulus for atrial dilation. Chronically, dilation and increased atrial compliance would tend to normalize pressure and explain the absence of a strong pressure-volume correlation in our population with chronic MR. Other factors confounding a good correlation may include the chronicity of the disease process, the response of atrial pressures to exercise, and disease altering the atrial wall (i.e., rheumatic involvement).

Potential study limitations: Angiographic semiquantitation of MR severity was the comparative standard of reference but this technique has several limitations. LA opacification is affected by factors independent of regurgitant volume, such as the amount of contrast delivered to the ventricle, the LV end-diastolic volume and the absolute atrial size.[31,32] These factors may lead to an overlap of regurgitant volumes and semiquantitative grades. Quantitative ventriculography may provide a better measure of regurgitant fraction but has its own limitations.[33] Clinically, the semiquantitative regurgi-

tant criteria we employed are widely used for decision-making.

It was necessary that MR be present on both the echocardiographic and angiographic study to avoid including regurgitation induced by catheter interference with the mitral valve apparatus. This definition would theoretically disqualify patients who had minimal MR detected only by Doppler examination. The absence of severe MR is rarely in doubt in this population; thus, their exclusion from the study has little clinical significance.

The time delay between angiography and echocardiography could allow loading conditions to vary despite our patients unchanged clinical status, and theoretically result in differing degrees of MR and chamber dimensions at each examination. Chronic MR was present in 93% of our patients, and the mean time between examinations was short at 2.8 days, with 50% being performed within 24 hours of each other. Thus, it would be expected that there was minimal variation in chamber dimensions and regurgitation severity.

Acknowledgment: We would like to thank Catherine Otto, MD, and Alan Pearlman, MD, for their helpful advice in the preparation of this manuscript.

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Pulmonary Venous Flow Dynamics Before and After Balloon Mitral Valvuloplasty as Determined by Transesophageal Doppler Echocardiography

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The pattern of left atrial filling was studied in 14 patients with severe mitral stenosis in sinus rhythm before and immediately after successful balloon mitral valvuloplasty by transesophageal pulsed Doppler echocardiography of the left superior pulmonary vein. Mean mitral valve orifice area increased from 0.8 ± 0.1 to 2.2 ± 0.3 cm^2 ($p < 0.0001$), and left atrial mean pressure decreased from 30 ± 5 to 12 ± 4 mm Hg ($p < 0.0001$) after the procedure. After balloon mitral valvuloplasty, significant increases in peak systolic pulmonary velocity (35 ± 16 to 44 ± 10 cm/s; $p < 0.01$), systolic flow velocity time integral (3.3 ± 1.5 to 5.9 ± 2.0 cm; $p < 0.001$) and the ratio of systolic/diastolic pulmonary venous flow velocity time integrals (0.8 ± 0.4 to 1.4 ± 0.5; $p < 0.001$) were observed. An acute increase in mitral valve orifice area caused no significant changes in peak diastolic forward flow velocity (40 ± 7 to 41 ± 9 cm/s; p = not significant [NS]), diastolic forward flow velocity time integral (4.3 ± 1.7 to 4.6 ± 1.8 cm; p = NS) and atrial flow reversal velocity (30 ± 3 to 35 ± 3 cm/s; p = NS) compared with at baseline. The results suggest that in patients with severe mitral stenosis and sinus rhythm, left atrial filling is biphasic with a diastolic preponderance, and successful mitral valvuloplasty is associated with an immediate increase in pulmonary venous systolic forward flow.

(Am J Cardiol 1992;70:780–784)

Pulmonary venous flow pattern is principally determined by left atrial events.[1–3] Normally, left atrial filling is pulsatile and occurs during ventricular systole (X wave) and diastole (Y wave). This is followed by a reversal of flow during atrial systole (Z wave). Pulmonary venous flow pattern is altered in patients with mitral stenosis, although conflicting data have been reported in this regard.[4,5] Recent data[6] suggested that in diastole, the left atrium acts as a conduit between the pulmonary veins and left ventricle, indicating that pulmonary venous diastolic forward flow is reduced in proportion to the severity of mitral stenosis.[4,5] Systolic flow velocity and velocity time integral have been shown to correlate with left atrial minimal volume and ejection fraction,[6] both of which are altered in mitral stenosis. A sudden increase in mitral valve orifice area should result in decreased orificial resistance and left atrial minimal volumes, with an improvement in left atrial ejection fraction. Thus, it is likely that left atrial inflow dynamics would change after balloon mitral valvuloplasty. In this study, we investigated the influence of a sudden increase in stenotic mitral valve area on the relative contribution of the 2 phases of pulmonary venous flow drainage to better understand the mechanics of left atrial filling, using the model of balloon mitral valvuloplasty.

METHODS

Patients: Fourteen consecutive patients (5 male and 9 female, mean age 20 ± 6 years, range 12 to 30) with severe mitral stenosis and sinus rhythm undergoing percutaneous balloon mitral valvuloplasty constituted the study group. Before the study, all patients underwent M-mode, 2-dimensional and Doppler echocardiography. No patient had mitral regurgitation.

Echocardiography: A complete M-mode, 2-dimensional and Doppler echocardiographic examination was performed in each patient immediately before cardiac catheterization and balloon valvuloplasty, using a commercially available ultrasound machine (CFM-750 VingMed, VingMed Sound A/S, Horten, Norway) and a dual-function 3.25/2.5 MHz annular array transducer. Transesophageal echocardiography was performed with a 5/4 MHz dual-frequency annular phased-array single-plane transducer in the cardiac catheterization laboratory using a previously reported technique.[7] Pulsed Doppler recordings of pulmonary venous flow were obtained by placing the sample volume (5 mm) 1 to 2 cm distal to the orifice of the left superior pulmonary vein, guided by color flow mapping. Baseline data were obtained immediately after transseptal puncture.

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TABLE I Pulmonary Venous Flow and Hemodynamic Variables in Patients Before and After Balloon Mitral Valvuloplasty

Pt. No.	Peak X (cm/s)		Peak Y (cm/s)		Peak Z (cm/s)		VTI X (cm)		VTI Y (cm)		VTI Z (cm)		LA Mean (mm Hg)		MVA (cm^2)	
	B	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A
1	20	46	41	47	19	24	2.4	6.3	4.8	5.9	1.2	1.8	25	9	0.6	2.6
2	46	52	47	38	27	23	3.7	5.9	3.3	2.9	2.0	1.2	28	15	0.8	1.9
3	37	39	42	25	20	26	4.4	3.6	4.8	1.7	2.1	2.4	38	15	0.8	2.4
4	25	57	40	52	17	40	2.3	6.3	4.7	4.1	1.1	2.6	31	7	0.9	1.8
5	79	48	48	38	55	37	7.4	10.0	4.9	7.9	4.8	3.3	30	10	1.0	3.0
6	22	48	25	40	16	16	1.5	4.7	2.0	3.6	1.0	1.0	27	12	0.8	1.9
7	45	57	33	45	18	40	4.1	6.1	2.3	3.5	1.1	2.2	28	16	0.6	2.0
8	28	49	44	57	18	20	3.2	5.6	7.5	5.7	1.2	1.1	35	13	0.8	2.2
9	37	47	41	49	22	22	4.4	6.8	7.4	6.9	1.3	1.2	35	11	0.8	2.0
10	25	26	27	27	129	134	3.2	3.3	2.9	2.9	1.3	1.3	35	13	0.9	2.2
11	26	35	35	35	22	24	1.6	3.7	2.7	3.6	1.7	2.0	25	11	1.0	2.6
12	39	36	44	36	—	—	3.2	6.6	3.9	3.1	—	—	32	12	0.6	2.1
13	42	46	45	42	19	27	3.3	9.7	4.0	5.9	1.3	1.9	26	7	0.8	2.2
14	21	28	46	40	22	21	1.7	5.1	4.8	6.2	1.3	1.7	35	20	0.6	1.9
Mean ±	35±	44±	40±	41±	30±	35±	3.3±	5.9±	4.3±	4.6±	1.6±	1.8±	30±	12.0±	0.8±	2.2±
SD	16	10	7	9	3	3	1.5	2.0	1.7	1.8	1.0	0.7	5	3.6	0.1	0.3
p value	<0.01		NS		NS		<0.001		NS		NS		<0.0001		<0.0001	

A = after valvuloplasty; B = before valvuloplasty; LA Mean = left atrial mean pressure; MVA = mitral valve area; NS = not significant; VTI = velocity time integral; X = systolic flow velocity; Y = early diastolic flow velocity; Z = flow velocity at atrial contraction.

The transesophageal probe was kept in place throughout the procedure and used to guide placement of guidewires and balloon catheters. Postprocedural Doppler data were recorded after balloon catheters were removed from the left atrium and replaced by a Cournand catheter. All 2-dimensional and Doppler echocardiographic data were recorded during quiet respiration on a ½ inch VHS videocassette recorder (Panasonic AG-6200, Panasonic Corp, Los Angeles, California). Furthermore, Doppler hard-copy recordings were obtained at a paper speed of 50 mm/s. Three consecutive beats were averaged for Doppler parameters.

Doppler echocardiographic measurements: Pulmonary venous flow velocity variables measured (Figure 1) included peak forward systolic (X) and diastolic (Y) flow velocities and their velocity time integrals, and peak reverse flow (Z) velocity and velocity time integral during atrial contraction. According to the 3 phases of pulmonary venous flow, velocity time integrals were measured as follows (Figure 1): Systolic velocity time integral was measured from the onset of forward flow to the crossover of that wave with the zero line. Diastolic forward flow velocity time integral was measured from the onset of this wave to its crossover with the zero line. The velocity spectrum of the combined forward systolic and diastolic flow was traced to measure the total forward flow velocity time integral. The velocity time integral of flow reversal due to atrial contraction was measured from onset to termination of negative flow velocities in late diastole.

Cardiac catheterization and balloon mitral valvuloplasty: All patients underwent standard right and left heart catheterization after overnight fast without any sedation. Parenteral fluid administration between the baseline and postprocedural echocardiographic studies was limited to 5% dextrose solution at 30 ml/hour. Hemodynamic measurements were obtained using a 7Fr end-hole catheter on the right side and a 7Fr pigtail catheter on the left side, referenced to midthoracic level, with the use of fluid-filled catheters and Gould transducers (Gould Electronics, Cleveland, Ohio). Left ventriculography was performed with an iodinated contrast

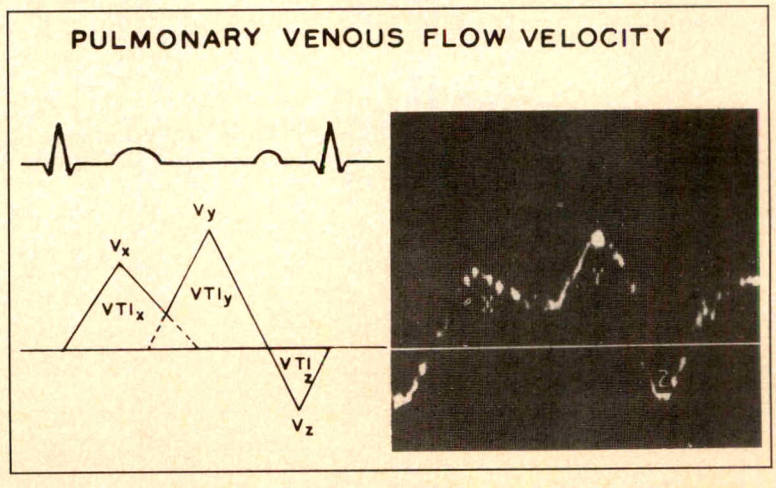


FIGURE 1. Velocity time profile of pulmonary venous flow and its *schematic diagram*. Pulmonary flow is triphasic and divided into systolic (X), early diastolic (Y) and atrial contraction (Z) phases. Variables measured included peak flow velocity during ventricular systole (V_x), peak forward flow velocity during ventricular diastole (V_y), peak reverse flow velocity associated with atrial contraction (V_z), velocity time integral of flow during ventricular systole (VTI_x), velocity time integral of forward flow during ventricular diastole (VTI_y), velocity time integral of reverse flow at time of atrial contraction (VTI_z), and velocity time integral of total forward flow.

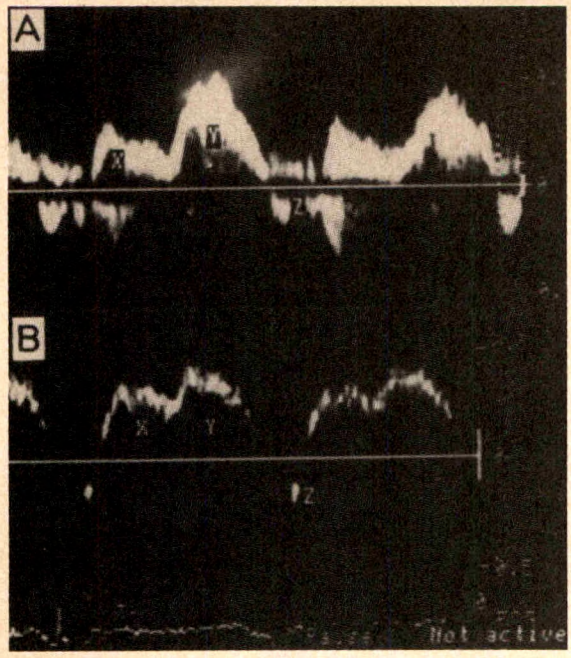


FIGURE 2. Pulmonary venous flow velocity recordings in patient immediately *(A)* before and *(B)* after successful balloon mitral valvuloplasty. Mitral valve area increased from 0.8 to 2.0 cm², and mean left atrial pressure decreased from 30 to 10 mm Hg. There were increases in peak velocity during ventricular systole (0.3 to 0.4 m/s) and velocity time integral during this phase (3.3 to 5.2 cm).

medium (20 to 25 ml, 76% urograffin) before the basal and after the postvalvuloplasty echocardiographic examinations. The technique of 2-balloon valvuloplasty was used.[8] Cardiac output was determined according to the Fick principle, and mitral valve area was calculated by the Gorlin formula.[9]

Statistical analysis: All values are expressed as mean ± 1 SD. Paired *t* test was used to study the difference in continuous variables. Pearson's correlation coefficients were calculated to relate Doppler echocardiographic and catheterization parameters. A 2-tailed p value <0.05 was considered significant.

RESULTS

Hemodynamic measurements: After balloon mitral valvuloplasty, there were significant decreases in mean left atrial pressure (30 ± 5 to 12 ± 4 mm Hg; p <0.001) and transmitral gradient (20 ± 6 to 6 ± 2 mm Hg; p <0.001), a small but significant increase in cardiac index (3.4 ± 1.2 to 3.7 ± 0.9 L/min/m²; p <0.05), and a large increase in mitral valve orifice area (0.8 ± 0.1 to 2.2 ± 0.3 cm²; p <0.0001). Mitral valvuloplasty was successful in all patients (≥50% increase in mitral valve area). Two patients developed mild (1+/4+) mitral regurgitation, and 12 had an iatrogenic atrial septal defect (<2 mm in diameter in all). There were no changes in heart rate (88 ± 10 to 86 ± 10 beats/min; p = not significant [NS]) and aortic systolic blood pressure (109 ± 10 to 104 ± 12 mm Hg; p = NS).

Pulmonary venous flow velocities (Table I): Balloon mitral valvuloplasty resulted in a significant increase in peak and integrated systolic pulmonary vein flow velocities, and systolic/diastolic peak velocity (0.9 ± 0.2 to 1.2 ± 0.1; p <0.01) and integral (0.8 ± 0.4 to 1.4 ± 0.5; p <0.001) ratios. Consequently, systolic/total forward flow (41 ± 12 to 58 ± 8%; p <0.001) and total forward flow integrals (8.1 ± 2.5 to 10.8 ± 3.7 cm; p <0.01) increased significantly. There was no change in peak diastolic velocity and flow integral. Figure 2 shows pulmonary venous flow velocity profiles in a patient before and immediately after valvuloplasty. Figure 3 depicts individual data on peak systolic velocities, and systolic

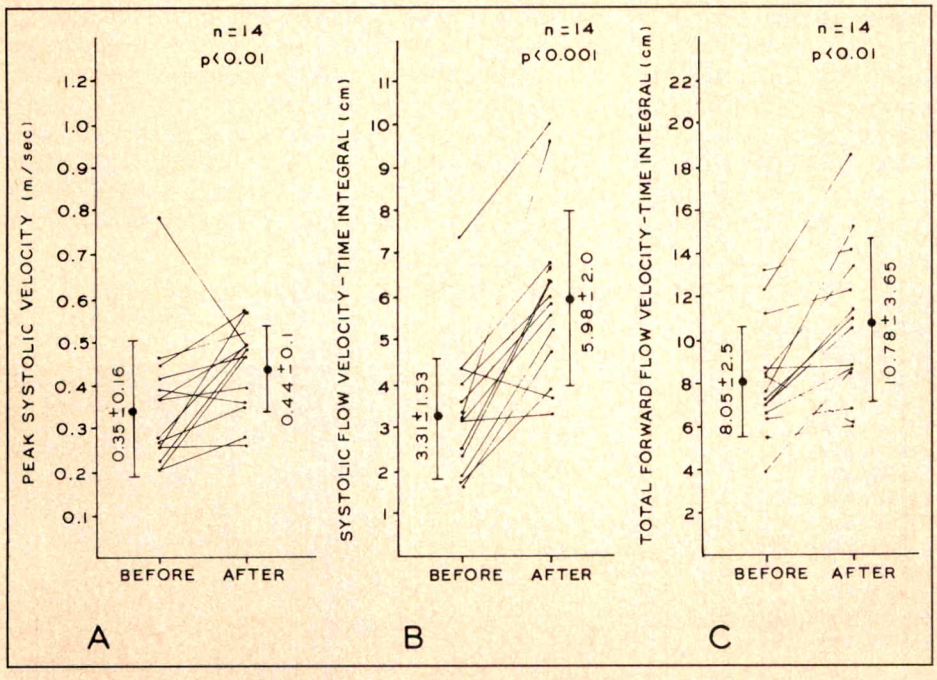


FIGURE 3. Effect of balloon mitral valvuloplasty on peak pulmonary venous flow velocity during ventricular systole *(A)*, velocity time integral of pulmonary flow during ventricular systole *(B)*, and velocity time integral of total forward flow *(C)* in 14 patients studied.

and total flow velocity time integrals before and after valvuloplasty. No significant correlation was found between mean left atrial pressure and various parameters of pulmonary venous flow velocities before and after valvuloplasty.

Intra- and interobserver variations: Interobserver errors for measurements of peak pulmonary venous flow velocities and flow integrals were 5 ± 2 and 9 ± 4%, respectively. Intraobserver variation was <5% for all measurements.

DISCUSSION

Pulmonary venous flow is pulsatile in mitral stenosis, and is determined largely by left atrial pressure[1] and mitral valve function.[4,5,10] Conflicting data have been reported regarding the pulmonary venous flow pattern in mitral stenosis.[4,5] A transthoracic pulmonary venous Doppler echocardiographic study showed that diastolic flow is reduced in mitral stenosis and becomes undetectable in severe cases.[4] In another study,[5] systolic forward flow velocity was found to be reduced with unaffected diastolic flow. Our data are similar to those of the latter study. In the basal state, pulmonary venous flow was biphasic with diastolic preponderance. Furthermore, systolic forward flow was monophasic, unlike the biphasic pattern in normal subjects.[5] Mitral stenosis caused a relative decrease in the proportion of left atrial filling occurring during ventricular systole and an absolute decrease in total pulmonary venous return to left atrium. Successful balloon mitral valvuloplasty resulted in an increase in the proportion of systolic and total forward flow. These changes were accompanied by marked reductions in mitral valve resistance (approximately 200% increase in mitral valve area), left atrial pressure and transmitral pressure gradients. In contrast, during ventricular diastole, no net change occurred in forward or reverse flow.

Pulmonary venous systolic flow: In patients with severe mitral stenosis, effective atrial function is markedly reduced.[11] Our unpublished observations suggest that the atrial contribution to left ventricular filling (determined by the method reported previously)[11] increases significantly after balloon mitral valvuloplasty ($n = 20$; 8 ± 3 vs $12 \pm 3\%$; $p < 0.001$). Marked diminution or loss of atrial systole may be an important factor causing a decrease in peak systolic velocity and systolic flow velocity time integral in severe mitral stenosis.[4] This is corroborated by the observation that pulmonary venous systolic flow velocity is reduced in atrial fibrillation.[3] A decrease in effective atrial contraction results in reduced or aborted atrial relaxation, and an improvement in atrial systolic function after balloon mitral valvuloplasty tends to reverse this phenomenon. This conclusion is also supported by a recent study[6] in which pulmonary venous systolic velocity and systolic flow velocity time integral were correlated to left atrial ejection fraction and minimal left atrial volume, both of which change favorably after balloon mitral valvuloplasty (unpublished observations). Furthermore, an increase in cardiac output after balloon valvuloplasty can increase systolic forward flow velocity.[12] Patients with chronic rheumatic heart disease and severe mitral stenosis have diminished left atrial compliance, which increases significantly immediately after mitral valvuloplasty.[13] Moreover, an increase in the systolic fraction of pulmonary venous flow immediately after valvuloplasty is possibly determined by the change in left atrial compliance. Increased systolic pulmonary venous flow associated with an increase in stenotic mitral valve orifice area in patients with mitral stenosis is unlikely to be related to the enhanced descent of the mitral annulus, because left ventricular systolic function remains unaffected after mitral valvuloplasty.[14,15]

Pulmonary venous diastolic forward and reverse flow: Pulmonary venous diastolic forward flow velocity has been variably reported to be normal[5] or reduced[4] in patients with mitral stenosis. We did not find any change in peak diastolic velocity or its time integral after balloon mitral valvuloplasty. Previous studies reported that the diastolic phase of pulmonary venous flow is affected by mechanics of the left ventricle.[5] Absence of any significant change in diastolic flow velocity with relief of mitral obstruction is consistent with the concept that the left atrium acts as a conduit between the pulmonary veins and left ventricle during diastole, with pulmonary venous flow largely determined by the same factors that influence early diastolic left ventricular filling.[6]

Study limitations: A potential limitation of a Doppler pulmonary venous flow study is that this method measures velocity and velocity time integral, and not absolute flow. Flow calculations need an estimate of the pulmonary vein cross-sectional area. Furthermore, the influence of mild mitral regurgitation and small iatrogenic atrial septal defects on pulmonary venous flows was not considered. However, mitral regurgitation tends to decrease systolic flow velocity,[5] and any effect of mitral regurgitation produced after balloon mitral valvuloplasty would only reinforce the conclusions delineated in this study. Finally, the patient cohort in this study had severe mitral stenosis with very high left atrial pressures. It is likely that changes in pulmonary venous velocities would vary with the degree of mitral stenosis.

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Relation Between Extent of Cardiac Muscle Cell Disorganization and Left Ventricular Wall Thickness in Hypertrophic Cardiomyopathy

Barry J. Maron, MD, James K. Wolfson, MD, and William C. Roberts, MD

The presence of numerous, abnormally arranged, cardiac muscle cells distributed widely throughout the hypertrophied left ventricular (LV) wall has been considered a characteristic, morphologic feature of patients dying of hypertrophic cardiomyopathy (HC) and also probably a determinant of impaired LV compliance. However, the relation between such regions of myocardial cell disarray and the magnitude of wall thickness in the same areas of the left ventricle has not been defined. Therefore, the present study was undertaken in which LV wall thickness and the percent area of myocardium disorganized were systematically compared in the same tissue section. No correlation was identified between wall thickness and the amount of myocardium disorganized in the same tissue sections, either when calculated separately for the ventricular septum, and anterolateral and posterior free walls, or when expressed for all 3 regions combined.

Therefore, in patients with HC: (1) disorganized myocardial architecture is not confined to greatly thickened portions of the LV wall, but regions of the left ventricle with normal or only mildly increased thickness may also be disordered; and (2) whereas both LV wall thickening and cellular disorganization are manifestations of the primary cardiomyopathic process, these 2 morphologic features do not appear to be directly related with regard to their extent and distribution within the LV wall. These observations will potentially enhance understanding of the relation between LV structure and compliance in HC.

(Am J Cardiol 1992;70:785–790)

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Hypertrophic cardiomyopathy (HC) is a primary cardiac disease characterized by an asymmetrically hypertrophied but nondilated left ventricle.[1] Disorganized arrangement of cardiac muscle cells has been recognized to be an important morphologic feature of the ventricular architecture in this disease.[2–13] It has also been generally accepted that in HC the thickest portions of the left ventricular (LV) wall are most likely to contain disordered myocardial cells. However, this relation between the magnitude of LV wall thickness and the degree of cardiac muscle cell disorganization has not been systematically investigated in HC. Therefore, the present investigation was performed using histologic sections obtained at necropsy from 31 patients with HC.

METHODS

Selection of patients: The cardiovascular registry of the National Heart, Lung, and Blood Institute was reviewed, and 31 hearts were included in the present study group. Each patient fulfilled our basic anatomic definition of HC with an asymmetrically hypertrophied nondilated left ventricle in the absence of another cardiac or systemic disease capable of producing the magnitude of LV hypertrophy present in that patient.[1] In 25 of 31 patients, typical clinical, hemodynamic, angiocardiographic and operative findings of HC[14,15] were also present; the other 6 had no cardiovascular evaluation during life, and sudden death was the first definitive manifestation of cardiac disease.[14–16]

The 31 study patients ranged in age from 11 to 61 years (mean 34); 16 (51%) were male. Before death, 9 patients were asymptomatic, 9 mildly symptomatic, and 13 severely symptomatic. Nineteen patients had the obstructive form of HC (outflow gradient ≥30 mm Hg during basal conditions or with provocative maneuvers), 6 were nonobstructive (gradient <30 mm Hg during basal conditions or with provocation), and the remaining 6 did not have cardiac catheterization. In the 25 patients with hemodynamic studies, maximal basal or provocable gradients ranged from 0 to 175 mm Hg (average 81).

Eighteen patients died suddenly (3 from progressive congestive heart failure, 8 at operation or cardiac catheterization, 1 of stroke, and 1 by suicide). Heart weights were 270 to 1,020 g (mean 592 ± 171) for the 24 adult patients (488 ± 111 g in 12 women, and 695 ± 160 g in 12 men). In the 7 children (aged 11 to 17 years), heart weights were 270 to 530 g.

Preparation of specimens: In each, full thickness tissue blocks were obtained from the LV wall in the transverse plane perpendicular to the long axis of the

ventricle (approximately half the distance between the apex and the base of the aortic valve) in the following 3 sites: (1) ventricular septum, (2) anterolateral free wall approximately 2 cm lateral to the left anterior descending coronary artery, and (3) posterior free wall between the papillary muscles. The tissue was imbedded in paraffin, sectioned at 6 μ thickness and stained with hematoxylin and eosin.

Maximal wall thickness was measured in each LV section from the fixed and stained tissue specimen with the use of calipers. Measurements were obtained perpendicular to the endocardial surfaces of the wall; care was taken to exclude trabeculae, papillary muscles, crista supraventricularis muscle and the endocardial contact plaque[17] from these measurements. Furthermore, tissue sections with transmural or extensive replacement fibrosis were excluded from this study.[18]

Definition and classification of abnormal cardiac muscle cell arrangement: Cardiac muscle cell disorganization was classified into 2 major types (Figure 1). Type I disorganization was the most frequent and usually consisted of areas of myocardium in which adjacent cells were aligned perpendicularly or obliquely to each other, forming tangled masses or "pinwheel" configurations. Although most of these lesions were small, the size of individual foci of disorganization varied greatly. Alternatively, type I disorganization comprised relatively broad bundles of muscle cells that were oriented at oblique or perpendicular angles to each other; cells within these bundles were, however, normally arranged.

Type II disorganization consisted of relatively narrow (usually 1 or 2 cells wide) longitudinally cut bundles of cells that were interlaced in various directions among larger groups of transversely cut cells (that appeared circular). This type of disorganization gave the myocardium a distinctive, "swirled" appearance.

Abnormally arranged cardiac muscle cells were not considered representative of true disorganization if present in the following areas where cells normally converge at acute angles: (1) at or near the junction of the ventricular septum with the left and right ventricular free walls; (2) in trabeculations; (3) in or at the edges of

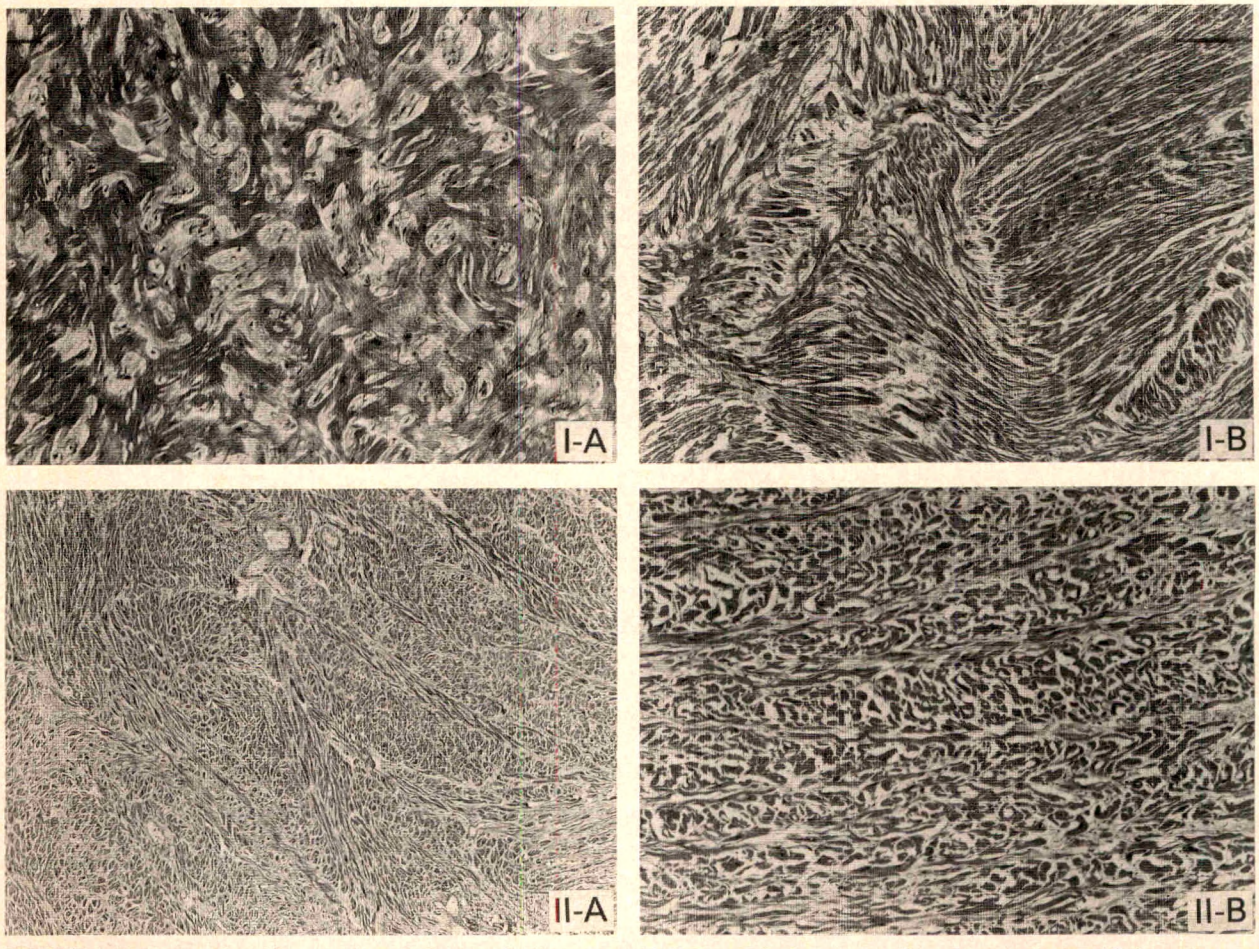


FIGURE 1. Patterns of cardiac muscle cell disorganization present in left ventricular myocardium from patients with hypertrophic cardiomyopathy. Type I exclusively involves cardiac muscle cells cut longitudinally. The most frequent pattern, designated here as type I-A, consisted of areas of myocardium in which adjacent cardiac muscle cells were aligned perpendicularly or oblique to each other. In type I-B, relatively broad bundles of muscle cells were oriented at oblique or perpendicular angles to each other. Type II involves cells cut either longitudinally or transversely. Type II-A consisted of relatively narrow bundles of cardiac muscle cells interlaced in various directions among other, larger groups of cells. Type II-B was similar except that disorganized bundles of cells were more linear in orientation. (Hematoxylin-eosin stain: I-A × 130, I-B and II-A × 40, II-B × 80; reduced by 26%.)

areas of fibrosis; (4) at points of convergence of major muscle bundles; or (5) adjacent to interstitial spaces containing blood vessels.

We did not attempt to assess the degree to which cells were malaligned in a given area of tissue. Disorganization was judged only to be present or absent and its severity was expressed in terms of extent.

Quantitation of cardiac muscle cell arrangement: A previously described technique[9] was used to quantitatively assess the extent to which cardiac muscle cell disorganization was present in each tissue section. Histologic sections were photographed and the images were enlarged to occupy 30 × 40 inch positive prints. A transparent cellulose overlay was then placed on the print. Areas of myocardium occupied by disorganized cardiac muscle cells were outlined on the overlay with a marking pen. We often could not obtain this assessment exclusively and directly from the print, and frequently had to reexamine the original tissue section with a light microscope to reliably identify the disorganized area. Furthermore, areas in which cardiac muscle cells were cut either longitudinally or transversely were demarcated; regions of fibrosis (replacement, interstitial and the endocardial contact plaque), artifacts of tissue preparation or large interstitial spaces with blood vessels were also outlined and ultimately excluded from the analysis. The transparent overlay was then removed from the print and photographed, and the image was reproduced (with substantial reduction) as a 5 × 7 inch positive print. Each area into which the tissue section had been divided was outlined separately with a fine-point marking pen on ordinary tablet paper. The area of each outlined silhouette was then quantitated using a video planimetry system.

Areas of tissue sections studied were 5.9 ± 2.7 cm^2 for the ventricular septum, 3.8 ± 1.8 cm^2 for the anterolateral free wall, and 2.8 ± 1.3 cm^2 for the posterior free wall.

Formulas used in quantitative calculations of cardiac muscle cell arrangement: The formulas used to calculate the percent area of tissue section occupied by disorganized cardiac muscle cells were as follows (the area of myocardium "at risk" for disorganization is in the denominator of both equations):

$$\% \text{ area of type I disorganization} = \frac{D_I}{L + D_I} \times 100$$

$$\% \text{ area of type II disorganization} = \frac{D_{II}}{L + T + D_{II}} \times 100$$

where L = area occupied by longitudinally cut but normally arranged cells, T = area occupied by transversely cut cells, D_I = area occupied by type I disorganization, and D_{II} = area occupied by type II disorganization. Percent disorganization plotted for each tissue section was the value for type I or II disorganization, whichever was greater. Values for types I and II disorganization could not be combined in patients with both types, because this calculation often resulted in a marked underestimation of the overall extent of disorganization present in a given tissue section.

Statistical analyses: Data were expressed as mean ± SD. Morphologic measurements between groups of patients were assessed by unpaired Student's *t* test. The relation between percent area of tissue section disorganized and LV wall thickness was assessed by linear regression analysis.

RESULTS

Left ventricular wall thickness: Measurement of LV wall thickness was greatest for the ventricular septum, ranging from 14 to 40 mm (mean 22). Anterolateral and posterior wall thicknesses were similar; anterolateral was 10 to 30 mm (mean 18), and posterior was 11 to 27 mm (mean 17). Wall thicknesses <15 mm were considered normal or virtually normal; such measurements were present in 1 ventricular septal tissue section, and 8 anterolateral and 10 posterior free wall sections.

Cardiac muscle cell disorganization: VENTRICULAR SEPTUM: The extent of cellular disorganization was greatest in the ventricular septum. The percent area of septum disorganized ranged from 0 to 95% (mean 40). Some disorganization was present in 30 patients (97%); disorganization constituted 5 to 24% of the relevant part of the tissue section in 8 patients (26%) and 25 to 49% in 6 patients (19%), and was particularly extensive involving ≥50% of the section in 13 patients (42%).

ANTEROLATERAL FREE WALL: Substantial cardiac muscle cell disorganization was also identified in the anterolateral free wall, with the percent area of tissue section disorganized ranging from 0 to 94% (mean 33). Some disorganization was present in 25 patients (81%); disorganization constituted 5 to 24% of the relevant part of the tissue section in 9 patients (29%) and 25 to 49% in 2 patients (6%), and was particularly extensive involving ≥50% of the section in 11 patients (36%).

POSTERIOR FREE WALL: In the posterior free wall, the percent area of tissue section disorganized ranged from 0 to 95% (mean 31). Some disorganization was present in 23 patients (74%); disorganization constituted 5 to 24% of the relevant part of the tissue section in 5 patients (19%) and 25 to 49% in 6 patients (19%), and was particularly extensive involving ≥50% of the section in 5 patients (16%).

In the 19 tissue sections studied (septum, and anterolateral and posterior free walls) with wall thickness <15 mm, the extent of cardiac muscle cell disorganization was 0 to 94% (mean 40 ± 32). In the 6 sections >30 mm in thickness, the extent of cellular disorganization was similar (range 9 to 59%, mean 36 ± 18; $p > 0.05$). In 28 tissue sections with <5% disorganization, wall thicknesses were 12 to 19 mm (mean 18 ± 4); in 28 sections with ≥50% disorganization, wall thicknesses were similar (range 11 to 40 mm, mean 19 ± 7; $p > 0.05$).

Relation between left ventricular wall thickness and extent of cardiac muscle cell disorganization: Comparison of LV wall thicknesses and percent area disorganized in the same tissue sections showed no correlation, either when calculated separately for the ventricular

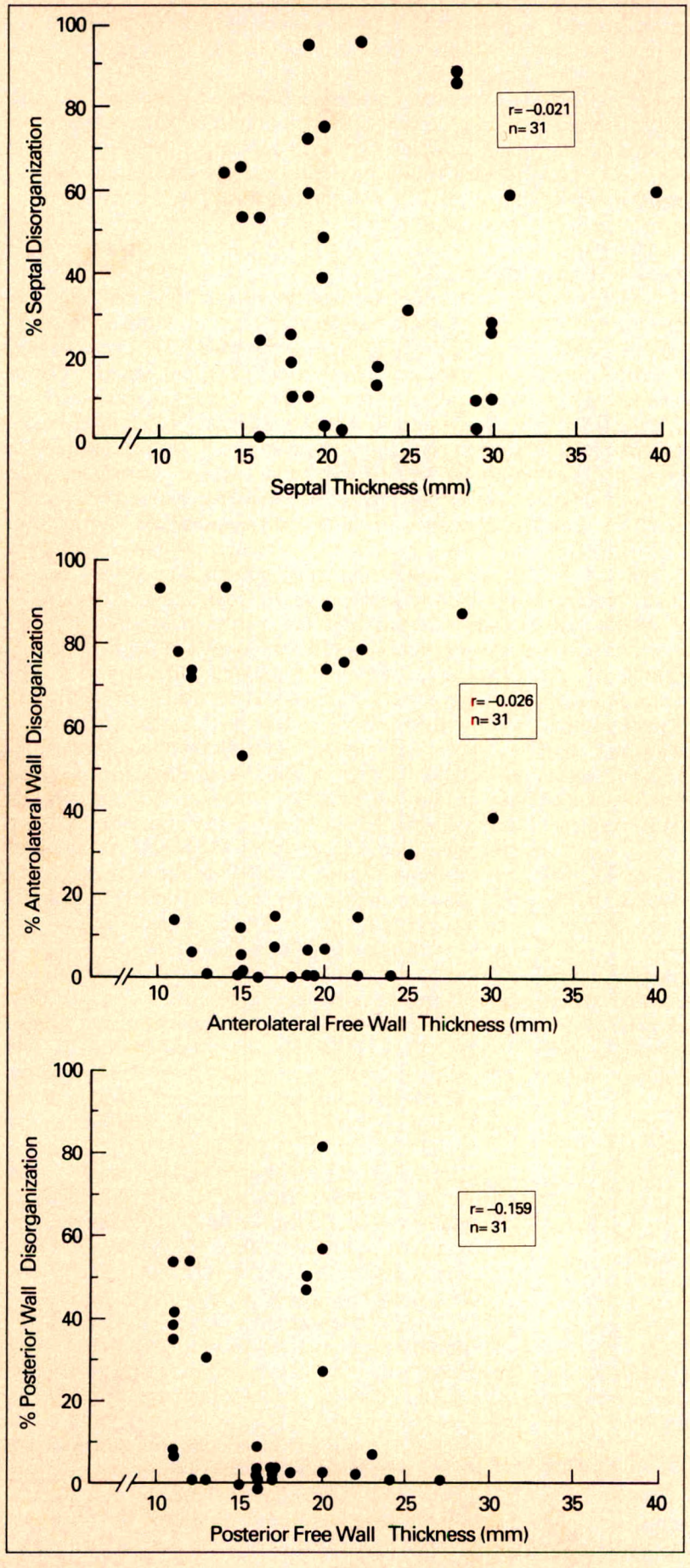


FIGURE 2. Relation between left ventricular wall thickness (in 3 sites) and extent of cardiac muscle cell disorganization in same tissue section from 31 patients with hypertrophic cardiomyopathy.

TABLE I Relation Between Cardiac Muscle Cell Disorganization and Left Ventricular Wall Thickness in 31 Patients with Hypertrophic Cardiomyopathy

LV Site	No. of Pts.	% Area Disorganized	Wall Thickness (mm)	r Value	Slope
Ventricular septum	31	40 ± 30 (0–95)	22 ± 6 (14–40)	−0.021	−0.101
Anterolateral free wall	31	33 ± 36 (0–94)	18 ± 5 (10–30)	−0.026	−0.188
Posterior free wall	31	19 ± 23 (0–81)	17 ± 4 (11–27)	−0.159	−0.863
All combined	93	31 ± 31 (0–95)	19 ± 5 (10–40)	−0.063	−0.342

LV = left ventricular.

septum, and anterolateral and posterior free walls (Figure 2), or when expressed for all 3 regions combined (Table I); correlation coefficients ranged from −0.021 to −0.159. Furthermore, no correlation was evident between LV wall thickness and either type I or II disorganization when assessed separately. No correlation was evident between total percent cellular disorganization and basal LV outflow gradient in the 25 patients with hemodynamic studies ($r = -0.08$).

DISCUSSION

We previously demonstrated that in patients dying of HC, disorganization of cardiac muscle cells is usually widely distributed throughout the LV wall.[6–10] The findings of the present study extend those observations and show that disordered myocardial architecture is not confined to greatly thickened portions of the ventricular myocardium, and that conversely, regions of normal or only mildly increased wall thickness also may be disorganized. For the overall group of patients studied, there was absolutely no statistical relation between the magnitude of LV wall thickness and the extent to which cardiac muscle cells within the same tissue section were disorganized, regardless of the particular region of the LV wall assessed (i.e., ventricular septum, or anterolateral or posterior free wall).

The clear inference of the data is that whereas both LV wall thickening and cellular disorganization appear to be manifestations of the primary cardiomyopathic process in HC,[15] these 2 morphologic features are not linked with respect to their extent and distribution. Our observation that LV segments of normal or only mildly increased thickness may have substantial regions of disorganization demonstrates that even the least hypertrophied portions of the LV wall may also be considered part of the primary myopathic process. This finding deviates from the previous morphologic perception that it is primarily the greatly hypertrophied portions of hearts with HC that show abnormal myocardial architecture.[19,20]

The significance of the disordered myocardial architecture characteristic of HC is uncertain, although it has been suggested that it may have an important role in producing increased ventricular chamber stiffness and impaired relaxation.[14,15,21] If myocardial disorganization has such pathophysiologic significance, then the present data would suggest that abnormalities in compliance may involve normal or relatively thin segments of the wall (as well as those with greater wall thickness), in sharp contrast to the widely held concept that impaired compliance in HC is closely related to particularly substantial LV wall thickening.[14,21] However, the observations in the percent morphologic study are also consistent with previous Doppler echocardiographic findings[22] that LV diastolic filling abnormalities in HC are largely independent of the magnitude of LV hypertrophy, and are also frequent in patients with only mild and localized hypertrophy.

We could not assess with precision the impact that connective tissue formation had on the relation between LV wall thickness and the extent of cellular disorganization in the same tissue section. First, by necessity, sections with substantial scarring[23–25] were excluded from the present analysis (because assessment of cardiac muscle cell arrangement was precluded), and second, a detailed quantitative assessment of the magnitude of interstitial, perivascular and replacement fibrosis was not part of the study design.

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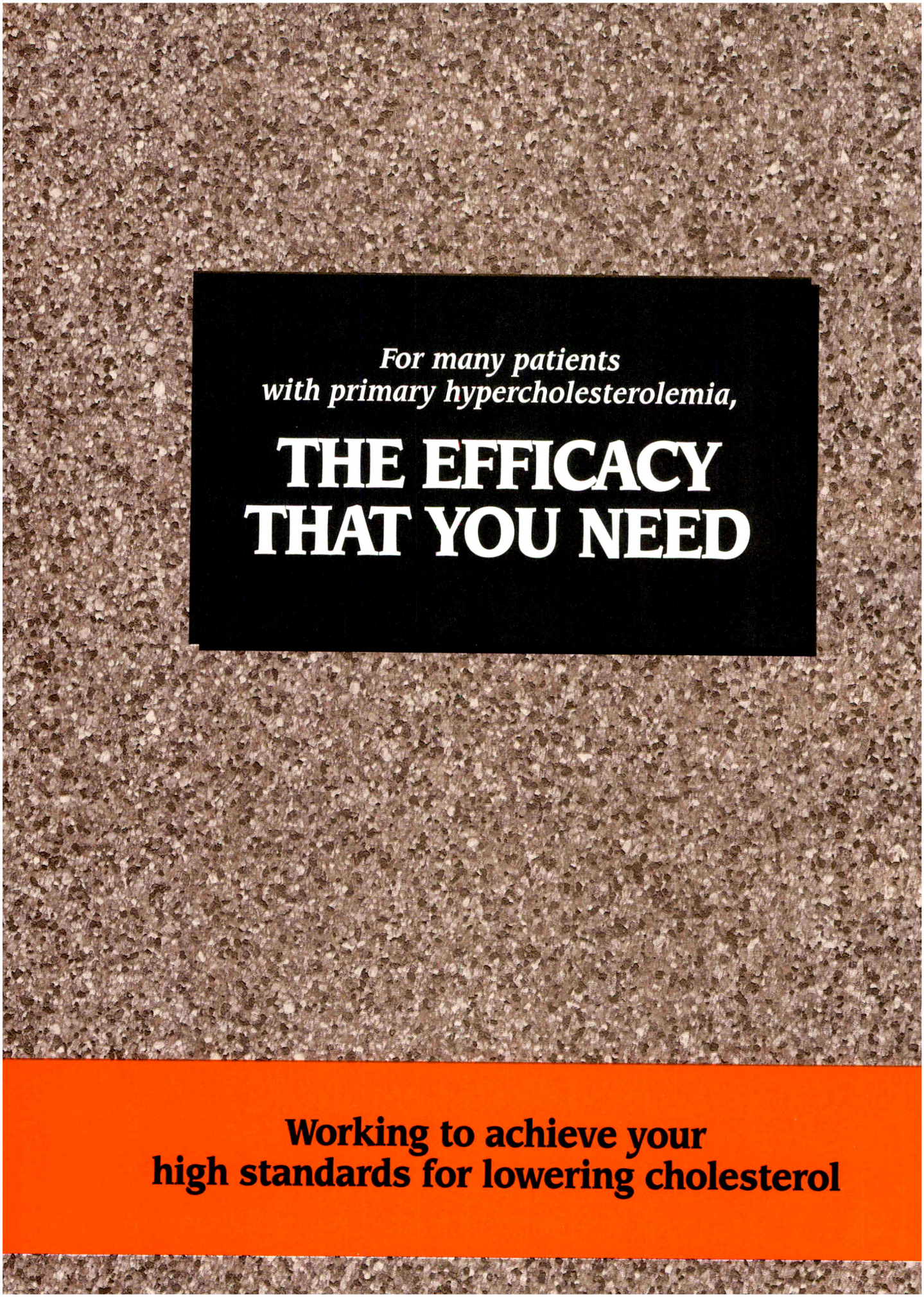
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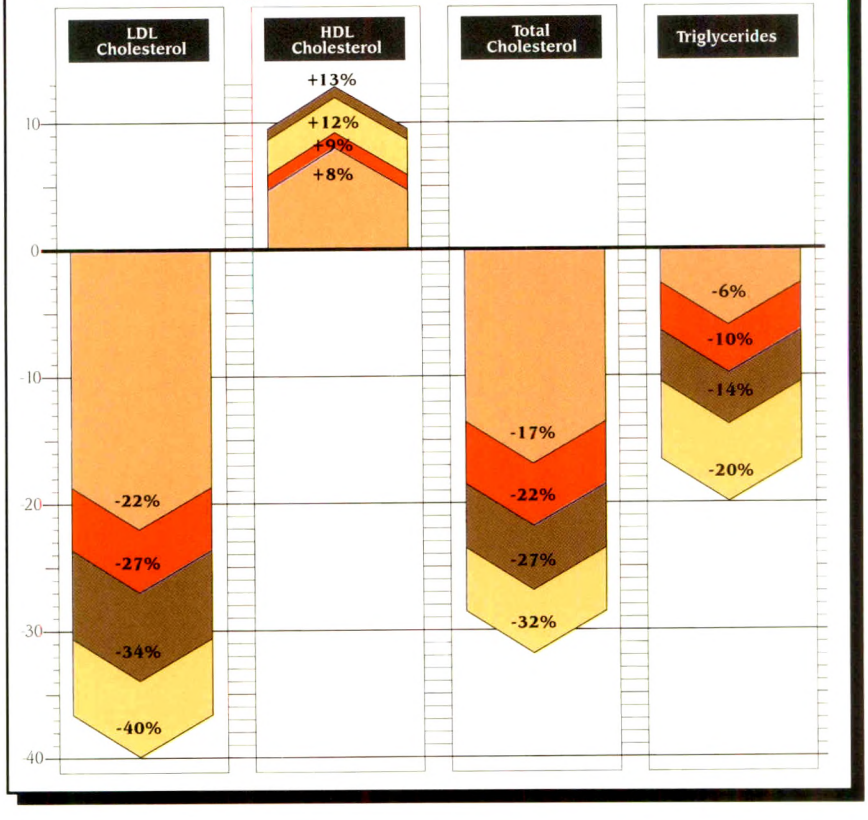
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CONTRAINDICATIONS: Hypersensitivity to any component of this medication.

Active liver disease or unexplained persistent elevations of serum transaminases (see WARNINGS).

Pregnancy and lactation. Atherosclerosis is a chronic process, and the discontinuation of lipid-lowering drugs during pregnancy should have little impact on the outcome of long-term therapy of primary hypercholesterolemia. Moreover, cholesterol and other products of the cholesterol biosynthesis pathway are essential components for fetal development, including synthesis of steroids and cell membranes. Because of the ability of HMG-CoA reductase inhibitors such as ZOCOR® (Simvastatin) to decrease the synthesis of cholesterol and possibly other products of the cholesterol biosynthesis pathway, ZOCOR may cause fetal harm when administered to a pregnant woman. Therefore, simvastatin is contraindicated during pregnancy and in nursing mothers. **Simvastatin should be administered to women of childbearing age only when such patients are highly unlikely to conceive.** If a patient becomes pregnant while taking this drug, simvastatin should be discontinued and the patient should be apprised of the potential hazard to the fetus.

WARNINGS: *Liver Dysfunction:* Persistent increases (to more than 3 times the upper limit of normal) in serum transaminases have occurred in 1% of patients who received simvastatin in clinical trials. When drug treatment was interrupted or discontinued in these patients, the transaminase levels usually fell slowly to pretreatment levels. The increases were not associated with jaundice or other clinical signs or symptoms. There was no evidence of hypersensitivity.

It is recommended that liver function tests be performed during therapy with simvastatin. Serum transaminase levels, including ALT (SGPT), should be monitored before treatment begins, every 6 weeks for the first 3 months, every 8 weeks during the remainder of the first year, and periodically thereafter (e.g., at approximately 6-month intervals). Special attention should be paid to patients who develop elevated serum transaminase levels, and in these patients, measurements should be repeated promptly and then performed more frequently. If the transaminase levels show evidence of progression, particularly if they rise to 3 times the upper limit of normal and are persistent, the drug should be discontinued. Liver biopsy should be considered if elevations persist beyond the discontinuation of the drug.

The drug should be used with caution in patients who consume substantial quantities of alcohol and/or have a past history of liver disease. Active liver diseases or unexplained transaminase elevations are contraindications to the use of simvastatin.

As with other lipid-lowering agents, moderate (less than 3 times the upper limit of normal) elevations of serum transaminases have been reported following therapy with simvastatin. These changes appeared soon after initiation of therapy with simvastatin, were often transient, were not accompanied by any symptoms, and did not require interruption of treatment.

Skeletal Muscle: Rare cases of rhabdomyolysis with acute renal failure secondary to myoglobinuria have been associated with simvastatin therapy. Rhabdomyolysis has also been associated with other HMG-CoA reductase inhibitors when they were administered alone or concomitantly with 1) immunosuppressive therapy, including cyclosporine in cardiac transplant patients; 2) gemfibrozil or lipid-lowering doses (≥1 g/day) of nicotinic acid in non-transplant patients; or 3) erythromycin in seriously ill patients. Some of the patients who had rhabdomyolysis in association with the reductase inhibitors had preexisting renal insufficiency, usually as a consequence of longstanding diabetes. In most subjects who have had an unsatisfactory lipid response to either simvastatin or gemfibrozil alone, the possible benefits of combined therapy with these drugs are not considered to outweigh the risk of severe myopathy, rhabdomyolysis, and acute renal failure. While it is not known whether this interaction occurs with fibrates other than gemfibrozil, myopathy and rhabdomyolysis have occasionally been associated with the use of other fibrates alone, including clofibrate. Therefore, the combined use of simvastatin with other fibrates should generally be avoided.

Physicians contemplating combined therapy with simvastatin and lipid-lowering doses of nicotinic acid or with immunosuppressive drugs should carefully weigh the potential benefits and risks and should carefully monitor patients for any signs or symptoms of muscle pain, tenderness, or weakness, particularly during the initial months of therapy and during any periods of upward dosage titration of either drug. Periodic creatine phosphokinase (CPK) determinations may be considered in such situations, but there is no assurance that such monitoring will prevent the occurrence of severe myopathy.

Because of an apparent relationship between myopathy and increased plasma levels of active metabolites derived from other HMG-CoA reductase inhibitors, the daily dosage should not exceed 10 mg/day in patients who are taking cyclosporine (see DOSAGE AND ADMINISTRATION in Prescribing Information).

Simvastatin therapy should be temporarily withheld or discontinued in any patient who has an acute, serious condition suggestive of a myopathy or who has a risk factor predisposing to the development of renal failure secondary to rhabdomyolysis (e.g., severe acute infection, hypotension, major surgery, trauma, severe metabolic, endocrine, and electrolyte disorders, and uncontrolled seizures).

Myopathy should be considered in any patient with diffuse myalgias, muscle tenderness or weakness, and/or marked elevation of CPK. Patients should be advised to report promptly unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever. Simvastatin therapy should be discontinued if markedly elevated CPK levels occur or if myopathy is diagnosed or suspected.

PRECAUTIONS: *General:* Before instituting therapy with ZOCOR, an attempt should be made to control hypercholesterolemia with appropriate diet, exercise, and weight reduction in obese patients and to treat other underlying medical problems (see INDICATIONS AND USAGE in Prescribing Information).

Simvastatin may cause elevation of CPK and transaminase levels (see WARNINGS and ADVERSE REACTIONS). This should be considered in the differential diagnosis of chest pain in a patient on therapy with simvastatin.

Homozygous Familial Hypercholesterolemia: ZOCOR is less effective in patients with the rare homozygous familial hypercholesterolemia, possibly because these patients have few functional LDL receptors.

Information for Patients: Patients should be advised to report promptly unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever.

Drug Interactions: *Immunosuppressive Drugs, Gemfibrozil, Niacin (Nicotinic Acid), Erythromycin:* See WARNINGS, *Skeletal Muscle.*

Antipyrine: Because simvastatin had no effect on the pharmacokinetics of antipyrine, interactions with other drugs metabolized via the same cytochrome isozymes are not expected.

Propranolol: In healthy male volunteers, there was a significant decrease in mean C_{max}, but no change in AUC, for simvastatin total and active inhibitors with concomitant administration of single doses of ZOCOR® (Simvastatin) and propranolol. The clinical relevance of this finding is unclear. The pharmacokinetics of the enantiomers of propranolol were not affected.

Digoxin: Concomitant administration of a single dose of digoxin in healthy male volunteers receiving simvastatin resulted in a slight elevation (less than 0.3 ng/mL) in digoxin concentrations in plasma (as measured by a radioimmunoassay) compared to concomitant administration of placebo and digoxin. Patients taking digoxin should be monitored appropriately when simvastatin is initiated.

Warfarin: Simvastatin therapy appeared to enhance slightly the anticoagulant effect of warfarin (mean changes in prothrombin time less than 2 seconds) in normal volunteers maintained in a state of low therapeutic anticoagulation. With other reductase inhibitors, clinically evident bleeding and/or increased prothrombin time has been reported in a few patients taking coumarin anticoagulants concomitantly. In such patients, prothrombin time should be determined before starting simvastatin and frequently enough during early therapy to insure that no significant alteration of prothrombin time occurs. Once a stable prothrombin time has been documented, prothrombin times can be monitored at the intervals usually recommended for patients on coumarin anticoagulants. If the dose of simvastatin is changed, the same procedure should be repeated. Simvastatin therapy has not been associated with bleeding or with changes in prothrombin time in patients not taking anticoagulants.

Other Concomitant Therapy: Although specific interaction studies were not performed, in clinical studies, simvastatin was used concomitantly with angiotensin-converting-enzyme (ACE) inhibitors, beta blockers, calcium channel blockers, diuretics, and nonsteroidal anti-inflammatory drugs (NSAIDs) without evidence of clinically significant adverse interactions. The effect of cholestyramine on the absorption and kinetics of simvastatin has not been determined.

Endocrine Function: HMG-CoA reductase inhibitors interfere with cholesterol synthesis and as such might theoretically blunt adrenal and/or gonadal steroid production. However, clinical studies have shown that simvastatin does not reduce basal plasma cortisol concentration or impair adrenal reserve and does not reduce basal plasma testosterone concentration (see CLINICAL PHARMACOLOGY, *Clinical Studies* in Prescribing Information). Another HMG-CoA reductase inhibitor has been shown to reduce the plasma testosterone response to HCG; the effect of simvastatin on HCG-stimulated testosterone secretion has not been studied.

Results of clinical trials with drugs in this class have been inconsistent with regard to drug effects on basal and reserve steroid levels. The effects of HMG-CoA reductase inhibitors on male fertility have not been studied in adequate numbers of male patients. The effects, if any, on the pituitary-gonadal axis in premenopausal women are unknown. Patients treated with simvastatin who develop clinical evidence of endocrine dysfunction should be evaluated appropriately. Caution should also be exercised if an HMG-CoA reductase inhibitor or other agent used to lower cholesterol levels is administered to patients who are also receiving other drugs (e.g., ketoconazole, spironolactone, cimetidine) that may decrease the levels or activity of endogenous steroid hormones.

CNS Toxicity: Optic nerve degeneration was seen in clinically normal dogs treated with simvastatin for 14 weeks at 180 mg/kg/day, a dose that produced mean plasma drug levels about 44 times higher than the mean drug level in humans taking 40 mg/day.

CNS vascular lesions, characterized by perivascular hemorrhage and edema, mononuclear cell infiltration of perivascular spaces, perivascular fibrin deposits, and necrosis of small vessels, were seen in dogs treated with simvastatin at a dose of 360 mg/kg/day, a dose that produced plasma drug levels that were about 50 times higher than the mean drug levels in humans taking 40 mg/day. Similar CNS vascular lesions have been observed with several other drugs of this class.

A chemically similar drug in this class also produced optic nerve degeneration (Wallerian degeneration of retinogeniculate fibers) in clinically normal dogs in a dose-dependent fashion starting at 60 mg/kg/day, a dose that produced mean plasma drug levels about 30 times higher than the mean drug level in humans taking the highest recommended dose (as measured by total enzyme inhibitory activity). This same drug also produced vestibulocochlear Wallerian-like degeneration and retinal ganglion cell chromatolysis in dogs treated for 14 weeks at 180 mg/kg/day, a dose that resulted in a mean plasma drug level similar to that seen with the 60 mg/kg/day dose.

Carcinogenesis, Mutagenesis, Impairment of Fertility: In a 72-week carcinogenicity study, mice were administered daily doses of simvastatin of 25, 100, and 400 mg/kg body weight, which resulted in mean plasma drug levels approximately 3, 15, and 33 times higher than the mean human plasma drug concentration (as total inhibitory activity) after a 40-mg oral dose. Liver carcinomas were significantly increased in high-dose females and in mid- and high-dose males, with a maximum incidence of 90% in males. The incidence of adenomas of the liver was significantly increased in mid- and high-dose females. Drug treatment also significantly increased the incidence of lung adenomas in mid- and high-dose males and females. Adenomas of the Harderian gland (a gland of the eye of rodents) were significantly higher in high-dose mice than in controls. No evidence of a tumorigenic effect was observed at 25 mg/kg/day. Although mice were given up to 500 times the human dose (HD) on a mg/kg body weight basis, blood levels of HMG-CoA reductase inhibitory activity were only 3 to 33 times higher in mice than in humans given 40 mg of ZOCOR.

In a separate 92-week carcinogenicity study in mice at doses of up to 25 mg/kg/day, no evidence of a tumorigenic effect was observed. Although mice were given up to 31 times the human dose on a mg/kg basis, plasma drug levels were only 2 to 4 times higher than in humans given 40 mg simvastatin as measured by AUC.

In a 2-year study in rats, there was a statistically significant increase in the incidence of thyroid follicular adenomas in female rats exposed to approximately 45 times higher levels of simvastatin than humans given 40 mg simvastatin (as measured by AUC). Preliminary results from a second 2-year rat study indicate an increase in the incidence of thyroid and liver tumors in male and female rats at doses that produce exposure levels ≥29 times (based on AUC) those achieved in humans at a dosage of 40 mg/day. Liver tumors are found in rodents with all the chemically similar drugs of this class. No increased incidence of tumors was observed at doses that produce exposure levels 15 times (based on AUC) those seen in man.

No evidence of mutagenicity was observed in a microbial mutagen test using mutant strains of *Salmonella typhimurium* with or without rat or mouse liver metabolic activation. In addition, no evidence of damage to genetic material was noted in an *in vitro* alkaline elution assay using rat hepatocytes, a V-79 mammalian cell forward mutation study, an *in vitro* chromosome aberration study in CHO cells, or an *in vivo* chromosomal aberration assay in mouse bone marrow.

There was decreased fertility in male rats treated with simvastatin for 34 weeks at 25 mg/kg body weight (15 times the maximum human exposure level, based on AUC, in patients receiving 40 mg/day); however, this effect was not observed during a subsequent fertility study in which simvastatin was administered at this same dose level to male rats for 11 weeks (the entire cycle of spermatogenesis including epididymal maturation). No microscopic changes were observed in the testes of rats from either study. At 180 mg/kg/day (which produces exposure levels 44 times higher than those in humans taking 40 mg/day), seminiferous tubule degeneration (necrosis and loss of spermatogenic epithelium) was observed. In dogs, there was drug-related testicular atrophy, decreased spermatogenesis, spermatocytic degeneration, and giant cell formation at 10 mg/kg/day (approximately 7 times the human exposure level, based on AUC, at 40 mg/day). The clinical significance of these findings is unclear.

Pregnancy: *Pregnancy Category X.* See CONTRAINDICATIONS.

Safety in pregnant women has not been established. Simvastatin was not teratogenic in rats at doses of 25 mg/kg/day or in rabbits at doses of up to 10 mg/kg daily. These doses resulted in 6 times (rat) or 4 times (rabbit) the human exposure based on mg/m² surface area. However, in studies with another structurally related HMG-CoA reductase inhibitor, skeletal malformations were observed in rats and mice. Simvastatin should be administered to women of childbearing potential only when such patients are highly unlikely to conceive and have been informed of the potential hazards. If a woman becomes pregnant while taking simvastatin, it should be discontinued and the patient should be advised again as to the potential hazards to the fetus.

Nursing Mothers: It is not known whether simvastatin is excreted in human milk. Because a small amount of another drug in this class is excreted in human milk and because of the potential for serious adverse reactions in nursing infants, women taking simvastatin should not nurse their infants (see CONTRAINDICATIONS).

Pediatric Use: Safety and effectiveness in children and adolescents have not been established. Because children and adolescents are not likely to benefit from cholesterol lowering for at least a decade and because experience with this drug is limited (no studies in subjects below the age of 20 years), treatment of children or adolescents with simvastatin is not recommended at this time.

ADVERSE REACTIONS: In the controlled clinical studies and their open extensions (2,423 patients with mean duration of follow-up of approximately 18 months), 1.4% of patients were discontinued due to adverse experiences attributable to ZOCOR® (Simvastatin). Adverse reactions have usually been mild and transient. ZOCOR has been evaluated for serious adverse reactions in more than 21,000 patients and is generally well tolerated.

Clinical Adverse Experiences: Adverse experiences occurring at an incidence of 1% or greater in patients treated with ZOCOR, regardless of causality, in controlled clinical studies are shown in the table below:

	ZOCOR (N=1,583)	Placebo (N=157)	Cholestyramine (N=179)	Probucol (N=81)
Body as a Whole				
Abdominal pain	3.2%	3.2%	8.9%	2.5%
Asthenia	1.6	2.5	1.1	1.2
Gastrointestinal				
Constipation	2.3	1.3	29.1	1.2
Diarrhea	1.9	2.5	7.8	3.7
Dyspepsia	1.1	—	4.5	3.7
Flatulence	1.9	1.3	14.5	6.2
Nausea	1.3	1.9	10.1	2.5
Nervous System/Psychiatric				
Headache	3.5	5.1	4.5	3.7
Respiratory				
Upper respiratory infection	2.1	1.9	3.4	6.2

The following effects have been reported with drugs in this class:

Skeletal: Myopathy, rhabdomyolysis, arthralgias.

Neurological: Dysfunction of certain cranial nerves (including alteration of taste, impairment of extraocular movement, facial paresis), tremor, vertigo, memory loss, paresthesia, peripheral neuropathy, peripheral nerve palsy, anxiety, insomnia, depression.

Hypersensitivity Reactions: An apparent hypersensitivity syndrome has been reported rarely which has included one or more of the following features: anaphylaxis, angioedema, lupus erythematous-like syndrome, polymyalgia rheumatica, vasculitis, purpura, thrombocytopenia, leukopenia, hemolytic anemia, positive ANA, ESR increase, arthritis, arthralgia, urticaria, asthenia, photosensitivity, fever, chills, flushing, malaise, dyspnea, toxic epidermal necrolysis, erythema multiforme, including Stevens-Johnson syndrome.

Gastrointestinal: Pancreatitis; hepatitis, including chronic active hepatitis, cholestatic jaundice, fatty change in liver, and, rarely, cirrhosis, fulminant hepatic necrosis, and hepatoma; anorexia; vomiting.

Skin: Alopecia.

Reproductive: Gynecomastia, loss of libido, erectile dysfunction.

Eye: Progression of cataracts (lens opacities), ophthalmoplegia.

Laboratory Abnormalities: Elevated transaminases, alkaline phosphatase, and bilirubin; thyroid function abnormalities.

Laboratory Tests: Marked persistent increases of serum transaminases have been noted (see WARNINGS, *Liver Dysfunction*). About 5% of patients had elevations of CPK levels of 3 or more times the normal value on one or more occasions. This was attributable to the noncardiac fraction of CPK. Muscle pain or dysfunction usually was not reported (see WARNINGS, *Skeletal Muscle*).

Concomitant Therapy: In controlled clinical studies in which simvastatin was administered concomitantly with cholestyramine, no adverse reactions peculiar to this concomitant treatment were observed. The adverse reactions that occurred were limited to those reported previously with simvastatin or cholestyramine. The combined use of simvastatin with fibrates should generally be avoided (see WARNINGS, *Skeletal Muscle*).

OVERDOSAGE: Significant lethality was observed in mice after a single oral dose of 9 g/m². No evidence of lethality was observed in rats or dogs treated with doses of 30 and 100 g/m², respectively. No specific diagnostic signs were observed in rodents. At these doses, the only signs seen in dogs were emesis and mucoid stools.

There have been no cases of clinically significant overdosage with ZOCOR in humans. Until further experience is obtained, no specific treatment of overdosage with ZOCOR can be recommended.

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J2ZO07R(902)

Effect of an Anterior Wall Motion Abnormality on the Results of Single-Plane and Biplane Left Ventriculography

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Although the biplane area-length method would be optimal for all left ventriculograms, 2 contrast injections are needed in laboratories with single-plane imaging equipment. The purpose of this study was to develop practical guidelines to identify the need for biplane left ventriculography in laboratories with single-plane equipment. From a retrospective analysis of 91 consecutive biplane ventriculograms (group 1), guidelines were identified that predicted when the ejection fraction calculated by the biplane method would differ significantly from the single-plane value. These guidelines were derived from information immediately available to the operator in the laboratory at the time of the procedure. Patients in group 1 were divided into 3 subgroups: biplane exceeding single-plane ejection fraction by ≥0.05 (n = 20); single-plane exceeding biplane ejection fraction by ≥0.05 (n = 14); and ejection fractions within ±0.04 by the 2 methods (n = 57). By multivariate analysis, the only predictor of a higher ejection fraction calculated by the biplane method was an anterior wall motion abnormality. This finding was tested prospectively in a separate group of 60 patients (group 2). Left ventriculograms in group 2 patients were stratified before analysis by the presence or absence of an anterior wall motion abnormality. In patients with anterior wall motion abnormalities, the biplane ejection fraction was greater than the single-plane value by 0.05 ± 0.04 (range −0.03 to +0.15). In contrast, this difference in patients without anterior wall motion abnormalities was −0.01 ± 0.04 (range −0.09 to +0.06; p <0.01). Therefore, in laboratories where only single-plane imaging is available, these data define a practical way to determine if a separate contrast injection in the left anterior oblique view would likely result in a higher value for the ejection fraction calculated by the biplane method.

(Am J Cardiol 1992;70:791–796)

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Biplane or single-plane left ventriculography is a standard part of cardiac catheterization. Validation studies generally have shown a good relation between single-plane and biplane volume estimates,[1–6] but in certain clinical situations, single-plane and biplane calculations of ejection fraction may differ substantially. For example, in patients with atrial septal defect, single-plane calculations overestimate the ejection fraction compared with biplane methods.[7] In contrast, other studies show that patients with coronary artery disease and left ventricular (LV) wall motion abnormalities often have higher ejection fractions when biplane rather than single-plane calculations are used.[8–10] Whereas the biplane method may be optimal,[11] many catheterization laboratories only have single-plane imaging systems. In this circumstance, a right anterior oblique ventriculogram usually is performed first, and the orthogonal view is obtained (at the operator's discretion) with a second contrast injection. The effort and potential risk of a second contrast injection would be worthwhile only if additional or different information were derived. Therefore, the purpose of this study was to develop practical guidelines to identify the need for biplane ventriculography in laboratories with single-plane equipment.

METHODS

Patient groups: Two different patient groups were used in this study. Group 1 comprised 100 consecutive patients referred for diagnostic cardiac catheterization in whom biplane left ventriculography was performed. Ventriculograms in 9 patients subsequently were excluded because they were technically inadequate for analysis. The remaining 91 studies were analyzed retrospectively to determine which findings might be predictive of a clinically important difference between the results of biplane and single-plane analyses. There were 64 men and 27 women (mean age 59 ± 13 years) in this group. The diagnoses determined by the procedure were coronary artery disease (n = 70), no detectable disease (n = 9), idiopathic dilated cardiomyopathy (n = 5), valvular heart disease (n = 4), pericardial disease (n = 1), congenital heart disease (n = 1) and prior cardiac transplantation (n = 1).

Left ventriculograms in group 1 were analyzed using both single-plane and biplane methods. Three subgroups were defined based on the difference between the biplane and single-plane ejection fractions. In 20 patients, the biplane ejection fraction exceeded the single-plane value by ≥0.05, in 14 patients the single-plane value exceeded the biplane value by ≥0.05 and, in the remaining 57 patients, the difference between the 2 val-

TABLE I Mean Left Ventricular Volumes and Ejection Fraction in Patient Groups

	Group 1 (n = 91)	Group 2 (n = 60)
Single-plane values		
End-diastolic (ml)	166 ± 58*	178 ± 64
End-systolic (ml)	85 ± 54*	84 ± 48
Ejection fraction	0.52 ± 0.17	0.55 ± 0.14
Biplane values		
End-diastolic (ml)	177 ± 61	179 ± 60
End-systolic (ml)	90 ± 57	81 ± 40
Ejection fraction	0.53 ± 0.16	0.55 ± 0.14

*p <0.002 compared with corresponding volumes within same group.

ues was <±0.04. To be useful, the guidelines should be available to the operator in the catheterization laboratory immediately after the single-plane study. Thus, the 9 variables assessed for the ability to predict the difference between the biplane and single-plane ejection fractions were LV wall motion as assessed visually in each of 5 segments from the ventriculogram, average wall motion score, single-plane end-diastolic and end-systolic volumes, and LV end-diastolic pressure. Single-plane volumes were included because digital subtraction techniques can provide these data rapidly after a contrast injection. End-diastolic pressure was included as a measure of diastolic performance.

Based on this analysis, the variable predictive of a greater ejection fraction by the biplane method was tested prospectively in group 2. This group comprised 60 consecutive patients (42 men and 18 women, mean age 59 ± 11 years) also referred for diagnostic catheterization. The diagnoses derived from the procedure were coronary artery disease (n = 46), no detectable disease (n = 7), idiopathic dilated cardiomyopathy (n = 2) and valvular heart disease (n = 5). To demonstrate that the biplane method would provide a result different than the single-plane method, all patients in group 2 underwent biplane ventriculography. The right anterior oblique ventriculogram was reviewed before the volume and ejection fraction calculations, and patients were stratified into 2 subgroups based on the guidelines developed from group 1. All studies were technically adequate for analysis. Volumes and ejection fraction were determined by an operator who was unaware of the guidelines developed from group 1.

Clinical variables: The presence and location of a prior myocardial infarction was identified, but only if there was a definite clinical event associated with the characteristic cardiac enzyme changes or Q waves on a 12-lead electrocardiogram.

Left ventriculography: Biplane left ventriculography was performed in 30° right and 60° left anterior oblique projections at a filming rate of 30 frames/s. A nonionic contrast agent was injected in the left ventricle at a rate of 10 to 15 ml/s for a total volume of 30 to 50 ml. All ventriculograms were viewed using a standard projector, and the outlines at end-diastole and end-systole were traced onto a piece of clear plastic film. Biplane left ventriculograms were analyzed by the area-length method[4] with the Wynne regression equation[5] excluding ectopic or postectopic beats. Single-plane ventriculography was performed by analyzing only the 30° right anterior oblique view using the area-length method with the Kennedy regression equation.[3] The ventricular outlines were digitized and volumes calculated using a commercial program (Digisonics CathPro Version 5.2). Correction for magnification was performed using a sphere of known diameter interposed in the x-ray field.[12]

Left ventricular end-diastolic pressure and wall motion: LV end-diastolic pressure was measured with a fluid-filled catheter system before contrast administration. LV wall motion was evaluated in the 30° right anterior oblique projection. Wall motion in each of 5 segments (anterobasal, anterior, apical, inferior and inferobasal) was assigned a value using the following scale: 0 = dyskinetic; 1 = akinetic; 2 = moderate/severe hypokinesia; 3 = mild hypokinesia; and 4 = normal. An average score was derived as the sum of the individual scores divided by 5.

Statistical analysis: Differences among continuous variables in Group 1 were evaluated by an analysis of variance followed by a multiple range test (Newman-Kuels). Other intergroup comparisons were made using a Student's *t* test, paired *t* test, or chi-square test as appropriate. Correlations between single and biplane measurements were performed by linear regression analysis. A multiple forward stepwise regression analysis was used to determine the variables predictive of a difference between the single and biplane calculations of ejection fraction. Data are reported as the mean ± standard deviation and a p value <0.05 was considered significant.

RESULTS

Comparison of biplane and single-plane volumes: Mean LV volumes and ejection fractions are listed in Table I. For patients in group 1, there were good correlations between biplane and single-plane LV end-diastolic volumes (biplane = 0.99 [single plane] + 11.2 ml; r = 0.94, SEE 19.4 ml, p <0.0001), end-systolic volumes (biplane = 1.03 [single plane] + 1.78 ml; r = 0.97, SEE 12.6 ml, p <0.0001) and ejection fractions (biplane = 0.91 [single plane] + 0.05; r = 0.95, SEE 0.05, p <0.0001). Mean end-diastolic and end-systolic volumes were slightly larger using the biplane calculations, but mean ejection fraction was not significantly different in group 1 patients.

Biplane versus single-plane ejection fractions (Table II): Based on the difference between biplane and single-plane ejection fractions in group 1 patients, 3 subgroups were defined. There were 14 patients in whom the single-plane ejection fraction exceeded the biplane value by ≥0.05 (biplane − single-plane ejection fraction ≥−0.05), and 20 patients in whom the biplane ejection fraction exceeded the single-plane value by ≥0.05 (biplane − single-plane ejection fraction ≥0.05). In most patients (n = 57), the difference between biplane and single-plane ejection fractions was considered minimal (range −0.04 to 0.04). Within each subgroup, LV volumes determined by the biplane method generally were larger than their single-plane counterparts (Table II).

TABLE II Left Ventricular Volumes, Ejection Fraction, End-Diastolic Pressure and Wall Motion Stratified by the Difference Between Biplane and Single-Plane Ejection Fractions

Biplane–Single-Plane Ejection Fraction	≥ −0.05 (n = 14)	−0.04 to +0.04 (n = 57)	≥ 0.05 (n = 20)
Single plane			
End-diastolic (ml)	160 ± 57*	166 ± 57*	171 ± 63*
End-systolic (ml)	74 ± 57*	83 ± 53*	100 ± 56
Ejection fraction	0.58 ± 0.14*	0.53 ± 0.17	0.43 ± 0.17*†
Biplane			
End-diastolic (ml)	170 ± 64	176 ± 61	186 ± 59
End-systolic (ml)	89 ± 67	88 ± 56	96 ± 54
Ejection fraction	0.51 ± 0.14	0.54 ± 0.16	0.51 ± 0.17
LVEDP (mm Hg)	16 ± 7	15 ± 7‡	20 ± 6
Wall motion score			
Anterobasal	3.8 ± 0.58	3.6 ± 0.8	3.6 ± 0.69
Anterior	3.4 ± 1.08	3.2 ± 1.12	2.4 ± 1.39
Apical	3.1 ± 1.33	3.0 ± 1.35	2.1 ± 1.61
Inferior	2.4 ± 1.22	3.1 ± 1.15	2.9 ± 1.35
Inferobasal	2.9 ± 1.03	3.4 ± 1.05	3.4 ± 1.14
Average	3.1 ± 0.78	3.3 ± 0.79	2.9 ± 0.95
Prior myocardial infarct	9/14 (64%)	22/57 (39%)	14/20 (70%)§
Anterior myocardial infarct	1/9 (11%)	7/22 (32%)	8/14 (57%)‖

*$p \leq 0.04$ compared with corresponding biplane value; †$p \leq 0.05$ compared with other groups; ‡compared with highest value; §$p < 0.03$; ‖$p < 0.05$.
LVEDP = left ventricular end-diastolic pressure.

Although ejection fractions were compared both within and between these subgroups, the differences detected were directly related to the definitions used to establish the subgroups. The difference between biplane and single-plane ejection fractions was poorly correlated ($r = 0.026$) with the biplane ejection fraction itself, indicating that the discrepancy in ejection fraction derived from the 2 techniques was not related to the level of ventricular performance.

Analysis of the wall motion scores within each subgroup is shown in Table II. In patients with a larger ejection fraction by the single-plane method, the inferior wall motion score was lower than the anterobasal score, but no differences were present among the other segments. In the subgroup with a larger ejection fraction by the biplane method, wall motion scores in the anterior and apical segments were lower than those in the anterobasal and inferobasal segments. When wall motion scores between subgroups were compared, the only difference found was a lower score in the anterior segment of patients with larger biplane ejection fractions. Finally, LV end-diastolic pressure was lower in those with a minimal difference between the ejection fractions than that of the subgroup with a higher ejection fraction by the biplane method.

Influence of prior infarction (Table II): The occurrence of a definite prior infarction was greater in those with disparate ejection fraction calculations compared with those who had a minimal difference between biplane and single-plane ejection fractions. In the subgroup with a higher ejection fraction by the single-plane method, 64% had a prior myocardial infarction, and in those with a higher ejection fraction by the biplane method, 70% had a prior infarction. In contrast, only 39% of patients with similar biplane and single-plane ejection fractions had a prior infarction ($p < 0.03$). When a prior infarction had occurred, patients with higher ejection fractions by the biplane method had more anterior myocardial infarctions (57%) than did those with higher ejection fractions by the single-plane technique (11%; $p = 0.04$).

Multivariate analysis: A forward stepwise regression analysis was performed on data from group 1 to determine the variables predictive of a difference between the biplane and single-plane ejection fractions. Of the 9 variables entered in the regression, only anterior wall motion score was predictive of the difference between the biplane and single-plane ejection fractions ($p = 0.02$; β coefficient -0.01). Therefore, as anterior wall motion score decreased, the difference between biplane and single-plane ejection fractions increased.

Prospective analysis of group 2: There were no differences in ventricular volumes or ejection fractions between groups 1 and 2, and in biplane and single-plane measurements within group 2 (Table I). In group 2, there was a good correlation between biplane and single-plane measurements of end-diastolic volume (biplane = 0.90 [single plane] + 19.7 ml; $r = 0.95$, SEE 18.1 ml, $p < 0.0001$), end-systolic volume (biplane = 0.81 [single plane] + 13.4 ml; $r = 0.97$, SEE 9.3 ml, $p < 0.0001$) and ejection fraction (biplane = 0.80 [single plane] + 0.11; $r = 0.83$, SEE 0.08, $p < 0.0001$).

The presence of an anterior wall motion abnormality as a guideline to determine whether the addition of the left anterior oblique view (biplane analysis) would result in a higher LV ejection fraction was tested prospectively in group 2 (Table III). To enable rapid and practical assessment of wall motion based on the videotape replay in the procedure room, anterior wall motion was simply described as normal or abnormal if any wall motion abnormality was present. Patients with abnormal wall motion ($n = 25$) had larger end-diastolic and end-systolic volumes and lower ejection fractions for both the single-plane and biplane measurements than did the subgroup with normal anterior wall motion ($n = 35$) (Table III). In the subgroup with normal anterior wall motion, there

were no differences among the biplane and single-plane measurements of volume and ejection fraction. The mean difference between the single-plane and biplane ejection fractions in these patients was −0.01 ± 0.04 (range −0.09 to +0.06). In the subgroup with abnormal anterior wall motion, single-plane and biplane end-diastolic volumes were similar, but single-plane end-systolic volumes were greater and ejection fractions less than the corresponding biplane measurements. The mean difference between biplane and single-plane ejection fractions in the presence of abnormal anterior wall motion was 0.05 ± 0.04 (range −0.03 to +0.15). This was significantly greater than the difference between ejection fractions in the subgroup with normal anterior wall motion (Figure 1).

TABLE III Prospectively Evaluated Patients Stratified According to Presence of Anterior Wall Motion Abnormality

Anterior Wall Motion	Normal (n = 35)	Abnormal (n = 25)
Single plane		
End-diastolic (ml)	157 ± 61	208 ± 57*
End-systolic (ml)	56 ± 34	123 ± 37*†
Ejection fraction	0.65 ± 0.08	0.41 ± 0.08*†
Biplane		
End-diastolic (ml)	157 ± 54	210 ± 56*
End-systolic (ml)	58 ± 28	114 ± 30*
Ejection fraction	0.64 ± 0.09	0.45 ± 0.07*
Biplane–single-plane ejection fraction	−0.01 ± 0.04	0.05 ± 0.04*

*p <0.01 compared with corresponding value in group with normal wall motion; †p <0.01 compared with biplane volume in this group.

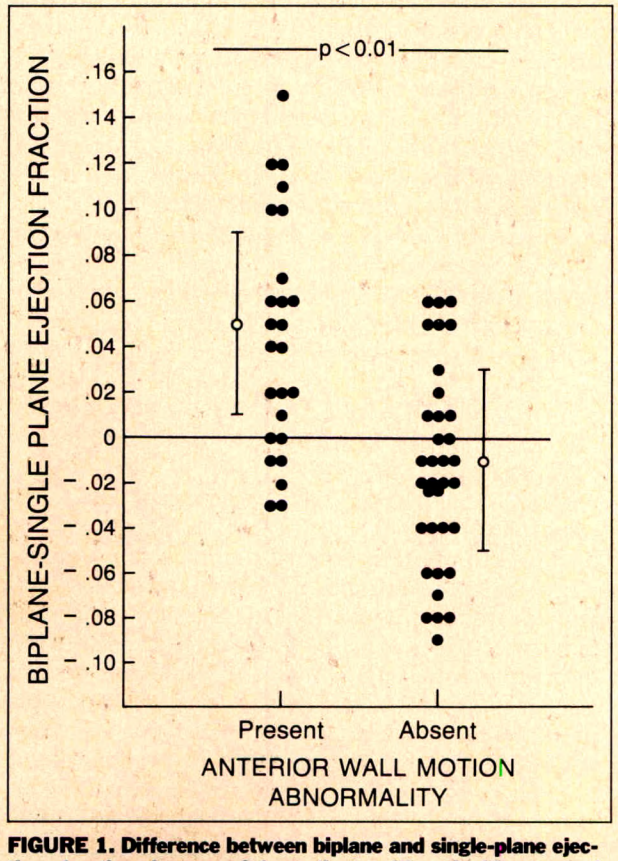


FIGURE 1. Difference between biplane and single-plane ejections fractions in group 2 for patients with and without anterior wall motion abnormality. Each *dot* represents value from individual patient. Mean and SD are shown to *side* of individual values.

DISCUSSION

Biplane and single-plane methods to calculate left ventricular volume: There are several angiographic methods to calculate LV volume.[1–5,13,14] Many of these methods assume that the LV chamber can be modeled by an ellipse whose dimensions are determined from the x-ray images. Dodge et al[4] introduced the biplane area-length method to avoid problems associated with the direct measurement of chamber diameters. With this technique, chamber diameters are calculated from the silhouette areas of the ventricle and long axis in each projection instead of measured directly.[5,15] The biplane area-length method was later modified for single-plane measurements.[2,3] The single-plane formula assumes that the 2 minor axes are of equal length and that the longest major axis of the left ventricle occurs in the right anterior oblique view. Validation studies of the single-plane method showed good correlations between biplane and single-plane volume measurements.[1–3] Compared with direct measurements from the biplane method, the assumed length of the unmeasured minor axis varied directly with the measured length, but averaged 7% less.[1] This resulted in single-plane volumes that were slightly larger than their biplane counterparts. Kennedy et al[3] also reported that single-plane volumes overestimated biplane volumes, but concluded that use of an appropriate linear regression equation could correct this problem.[3] However, these early validation studies were performed in patients without coronary artery disease.

Comparisons between the biplane and single-plane methods: Several studies subsequently compared biplane and single-plane volume measurements in specific clinical circumstances. In patients with right ventricular enlargement resulting from either mitral valve disease or left-to-right shunts, the long axis of the left ventricle is shifted posteriorly and the LV chamber is compressed.[16] This results in an overestimation of end-diastolic and end-systolic volumes and ejection fraction by the single-plane method compared with biplane values.[7] This discrepancy was caused by an inequality in the lengths of the minor axes of the left ventricle; in these patients, the minor axis in the left anterior oblique projection was 17% shorter than in the right anterior oblique view. Similar findings have been observed in patients with chronic pulmonary hypertension.[17]

Relatively few comparisons of single-plane and biplane volume calculations have been performed in patients with coronary artery disease. Cohn et al[8] compared biplane and single-plane results in 10 patients without and 50 with coronary artery disease. In patients without coronary artery disease, there was close agreement between the volumes and ejection fractions determined by the single-plane and biplane formulas. More disparity in volumes and ejection fractions were observed in patients with coronary artery disease, especially those with ventricular asynergy. The average difference in ejection fraction between the 2 techniques was 0.04 in patients without asynergy compared with 0.08 in

those with asynergy. These observations have been indirectly confirmed by comparing stroke volumes determined by ventriculography with those determined by Fick or indicator-dilution methods.[18] In patients without coronary artery disease and a normal or depressed LV ejection fraction, stroke volume determined by ventriculography closely approximated that measured by the other methods. However, in patients with LV ejection fractions <0.50 and extensive wall motion abnormalities, there was a poor relation between the angiographically derived stroke volume and the Fick- or indicator-dilution–derived stroke volume.[18] The poor relation in patients with abnormal wall motion suggests that the LV volumes used to calculate stroke volume were inaccurate, and this highlights the inaccuracies of the single-plane method in this subgroup of patients.

Results of the present study: Similar to prior validation studies, we found an excellent overall correlation between single-plane and biplane measurements of LV volume and ejection fraction in our study cohort.[1–6] However, there were important differences in some patients. The discrepancy between the 2 techniques was not simply related to the level of LV performance, because there was a poor correlation between the difference in ejection fraction values and the actual biplane ejection fraction. The largest discrepancies in ejection fraction between the 2 methods were not confined to patients with the lowest ejection fractions. When 9 variables available to the operator were assessed, we found that a difference between the single-plane and biplane ejection fractions was best predicted by an anterior wall motion abnormality. This finding was tested prospectively and confirmed. In patients with normal anterior wall motion, the mean difference between biplane and single-plane ejection fractions was -0.01 ± 0.04. In contrast, patients with abnormal anterior wall motion had a mean difference of 0.05 ± 0.04 between biplane and single-plane ejection fractions. Both end-diastolic and end-systolic volumes were larger in patients with anterior wall motion abnormalities. This is not surprising, because abnormal anterior wall motion suggests a prior anterior infarction occurred that could cause ventricular dilation. In patients with anterior wall motion abnormalities, end-diastolic volumes derived from the biplane and single-plane methods were similar, but single-plane end-systolic volumes were larger than their biplane counterparts. In the presence of decreased anterior wall motion, the minor axis of the left ventricle during systole (as measured from the right anterior oblique projection) would be longer than if wall motion were normal. With the single-plane method, the increased dimension is assumed to also be the dimension of the left ventricle in the orthogonal plane. This results in a greater end-systolic volume and lower ejection fraction compared with the biplane method where this dimension is actually measured. Although we did not directly measure the minor axis, the observed changes in end-systolic volume suggest that the assumptions made concerning the minor axis with the single-plane method could explain the differences in ejection fraction. Although anterior wall motion was found to be a predictor of the difference in ejection fractions between the 2 methods, inferior wall motion was not predictive. There are 2 possible explanations for this observation. First, inferior wall motion abnormalities identified in the right anterior oblique view often extend to the posterolateral wall. Therefore, the discrepancy between the assumed and actual length of the minor axis may be less in this circumstance, and the ejection fractions from the 2 methods will be similar. Second, it is possible that inferior wall motion was not predictive, because, in general, inferior infarctions have a lesser impact on LV ejection fraction than do anterior infarctions.[19]

Clinical implications: For the angiographer working in a single-plane laboratory, these data provide a simple and practical means to determine the usefulness of an additional contrast injection to obtain the orthogonal view so that the biplane formula may be used to calculate LV ejection fraction. These data show that in the presence of an anterior wall motion abnormality, ejection fraction averages 0.05 higher if the biplane method is used, and may be as much as 0.15 higher. Numerous important clinical studies, particularly those evaluating thrombolytic therapy or coronary revascularization, have used only the single-plane right anterior oblique method to measure ejection fraction.[20–23] Many patients included in these studies had anterior infarctions, and LV ejection fraction was used as one of the major outcome variables. Thus, the results of this study could have implications for the design of future angiographic studies in patients with coronary artery disease where LV ejection fraction is used as an end point.

Acknowledgment: The support of the technical staff of the C.V. Richardson Cardiac Catheterization Laboratory at the University of North Carolina Hospitals is gratefully acknowledged.

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An Improved Method for Adjusting the QT Interval for Heart Rate (the Framingham Heart Study)

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Several formulas have been proposed to adjust the QT interval for heart rate, the most commonly used being the QT correction formula ($QT_c = QT/\sqrt{RR}$) proposed in 1920 by Bazett. The QT_c formula was derived from observations in only 39 young subjects. Recently, the adequacy of Bazett's formula has been questioned. To evaluate the heart rate QT association, the QT interval was measured on the initial baseline electrocardiogram of 5,018 subjects (2,239 men and 2,779 women) from the Framingham Heart Study with a mean age of 44 years (range 28 to 62). Persons with coronary artery disease were excluded. A linear regression model was developed for correcting QT according to RR cycle length. The large sample allowed for subdivision of the population into sex-specific deciles of RR intervals and for comparison of QT, Bazett's QT_c and linear corrected QT (QT_{LC}). The mean RR interval was 0.81 second (range 0.5 to 1.47) heart rate 74 beats/min (range 41 to 120), and mean QT was 0.35 second (range 0.24 to 0.49) in men and 0.36 second (range 0.26 to 0.48) in women. The linear regression model yielded a correction formula (for a reference RR interval of 1 second): $QT_{LC} = QT + 0.154\ (1 - RR)$ that applies for men and women. This equation corrects QT more reliably than the Bazett's formula, which overcorrects the QT interval at fast heart rates and undercorrects it at low heart rates. Lower and upper limits of normal QT values in relation to RR were generated. A simple linear equation was developed that is more accurate than Bazett's correction at different cycle lengths and more convenient for clinical practice. This formula alleviates the need to apply secondary corrections to Bazett's formula. Additional investigation is warranted to determined whether QT_{LC} improves the identification of subjects at high risk for malignant arrhythmias or sudden death.

(Am J Cardiol 1992;70:797–801)

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Prolongation of the QT interval is associated with increased risk for malignant ventricular arrhythmias and sudden cardiac death in congenital long QT syndromes, electrolyte disturbances, after use of several antiarrhythmic drugs and after myocardial infarction.[1–12] The duration of the QT interval has been shown to depend on the length of the preceding cardiac cycle. It has been over 70 years since a formula for correcting QT for cycle length (QT_c) was introduced by Bazett.[13] However, the adequacy of this approach (dividing the measured QT by the square root of the measured RR) to adjust correctly for differences in heart rate has been questioned.[14–20] Although many formulas have been proposed to adjust the QT interval for heart rate, only a few have been derived or validated in a large population-based cohort.[14–22] In the present study we examined the initial baseline electrocardiogram in over 5,000 persons originally enrolled in the Framingham Heart Study. This report examines the relation of QT (and QT_c) to heart rate and presents results of a linear regression equation (QT_{LC}) that better corrects QT for heart rate.

METHODS

The original cohort of the Framingham Heart Study consisted of 5,209 subjects who were between the ages of 28 and 62 years on entering the study >40 years ago. The initial electrocardiograms of these subjects were used to measure the duration of the QT interval. From 1985 to 1986 all initial electrocardiograms were measured manually by 2 trained readers with the aid of calipers and magnifying lens. Measurements were obtained from a 12-lead resting electrocardiogram, with a paper speed of 25 mm/s. The average of 2 to 3 QT intervals from the electrocardiographic lead with the longest QT interval was analyzed. The QT interval was measured from the beginning of the QRS complex to the end of the T wave where its terminal limb joined the baseline. Each week a blinded duplicate review was performed on a random sample of all electrocardiograms read during that week. There was a high degree of inter- and intraobserver agreement. Any disagreements found were subsequently adjudicated and corrected. Additionally, a sample of 480 baseline electrocardiograms were blindly and independently reread 5 times. A high degree of correlation was obtained between the multiply read samples and the singly read baseline measurements with regard to the mean RR, and average QT interval ($p < 0.001$). Subjects with coronary heart disease ($n = 82$) at the initial examination were excluded from consideration because coronary disease may have affected the

TABLE I Characteristics of Study Population

	Men	Women	Total
Age (years)	44 ± 8.6	44 ± 8.5	44 ± 8.6
(range)	(29–62)	(28–62)	(28–62)
Heart rate (beats/min)	74 ± 12	77 ± 12	76 ± 12
(range)	(41–120)	(43–120)	(41–120)
RR interval (sec)	0.84 ± 0.14	0.80 ± 0.12	0.81 ± 0.13
(range)	(0.50–1.47)	(0.50–1.38)	(0.50–1.47)
QT interval (sec)	0.35 ± 0.03	0.36 ± 0.03	0.35 ± 0.03
(range)	(0.24–049)	(0.26–0.48)	(0.24–0.49)

Values are means ± standard deviation.

duration of the QT interval. In addition, subjects taking antiarrhythmic drugs or tricyclic antidepressants that might have affected the QT interval (n = 2) were also excluded. An additional 21 subjects were excluded because of extreme values for the RR interval (<0.5 or >1.5 seconds), because there were not enough data for analyses at the extremes. Finally, subjects with missing baseline electrocardiograms were also excluded (n = 84). After these exclusions, a total of 5,018 persons (2,239 men and 2,779 women) formed the study sample.

Data analysis: Least-squares multiple regression[23] was used for modeling the QT-RR relation in men and women. Analyses were performed on a SUN Sparc Station 1 running version 6.07 SAS software.[24] At first, separate models were fitted for each sex, but their similarities allowed us to combine men and women for subsequent analyses. The influence of RR, sex and age were examined through stepwise selection applied to RR interval, sex, age, RR^2 (to accommodate a curvilinear QT-RR relation), and sex · RR, sex · age, RR · age and sex · RR · age to accommodate higher-order influences. The final choice was the linear model that produces 2 regression lines: $QT = B_0 + B_1 \cdot RR + B_2 \cdot$ male, where male is a 0 to 1 indicator for male sex.

Linearity of the QT-RR relation was demonstrated by grouping subjects by sex-specific decile values of RR intervals and by plotting the mean QT versus mean RR for each decile. The fitted linear regression lines were overlaid for comparison. To approximate the typical 95% range of QT values that might be observed, we constructed 95% prediction intervals for persons at specified RR values. A table of lower and upper limits is presented.

An RR interval of 1.00 was selected as the reference point for the linearly corrected QT. Since Bazett's "formula" $QT_c = QT/(\sqrt{RR})$ is widely used, we applied both methods to the data for each subject and plotted mean values after grouping subjects by sex-specific RR deciles as mentioned before. This indicated whether each method corrected QT evenly across the range of RR values.

To see whether other nonlinear expressions for the QT-RR relation were better than the linear model, we also fitted several alternatives motivated by a prior investigation by Puddu et al.[17] Goodness-of-fit of the predicted values to the observed data was assessed visually by overlaying several curves, and quantitatively by lack of fit statistics and root-mean-squared errors (RMSE).

RESULTS

Subjects: Characteristics of the sample are summarized in Table I. The mean age of 44 years was the same for men and women. Women had shorter mean RR, faster heart rate and longer QT intervals than men.

QT-RR regressions: Separate QT-RR regressions for men and women produced similar results (fitted QT = 0.228 + 0.147 · RR, RMSE = 0.0220 and R squared = 0.467 for men; fitted QT = 0.227 + 0.167 ·

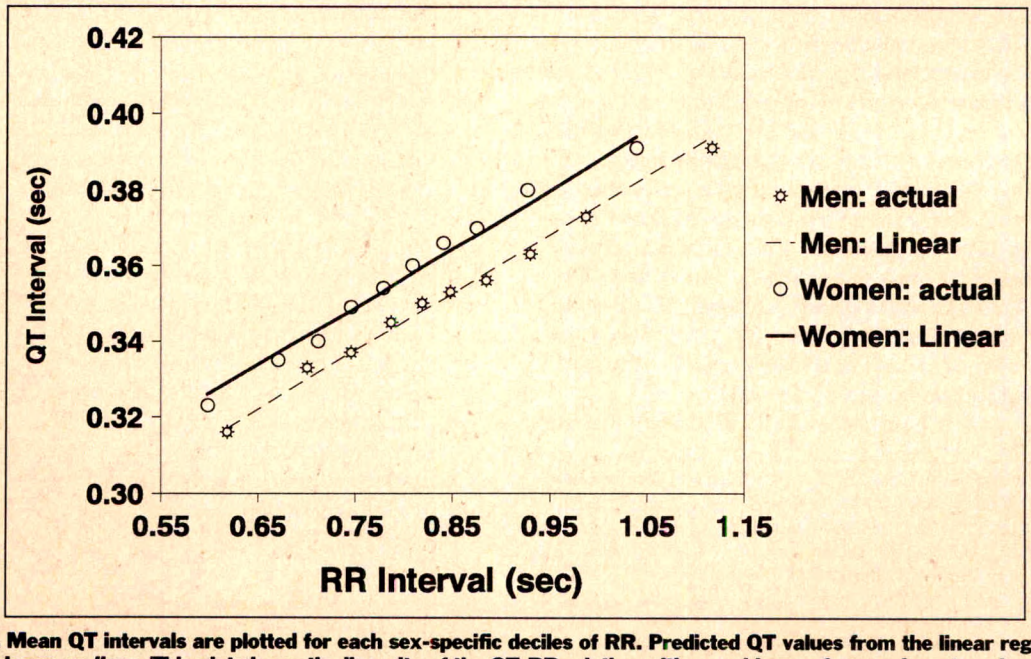


FIGURE 1. Mean QT intervals are plotted for each sex-specific deciles of RR. Predicted QT values from the linear regression model are shown as *lines*. This plot shows the linearity of the QT-RR relation with no evidence of gross departure from the fitted lines at any RR point either in men or women. These data were obtained from 2,239 male and 2,779 female cohort subjects.

TABLE II Mean QT, QT_c and QT_{LC} at Different Deciles of RR Interval in Men

RR Deciles (sec)	Heart Rate (beats/min)	No. of Men	Mean QT	Mean QT_c	Mean QT_{LC}
0.50–0.67	90–120	246	0.316	0.402	0.375
0.68–0.72	83–88	228	0.333	0.398	0.379
0.73–0.76	79–82	238	0.337	0.391	0.377
0.77–0.80	75–78	276	0.345	0.389	0.378
0.81–0.83	72–74	171	0.350	0.387	0.378
0.84–0.86	70–71	220	0.353	0.384	0.377
0.87–0.90	67–69	219	0.356	0.379	0.374
0.91–0.95	63–66	206	0.363	0.377	0.374
0.96–1.02	59–63	219	0.373	0.376	0.375
1.03–1.47	41–58	216	0.391	0.370	0.373

TABLE III Mean QT, QT_c and QT_{LC} at Different Deciles of RR Interval in Women

RR Deciles (sec)	Heart Rate (beats/min)	No. of Women	Mean QT	Mean QT_c	Mean QT_{LC}
0.50–0.64	94–120	303	0.323	0.417	0.385
0.65–0.69	87–92	315	0.335	0.409	0.386
0.70–0.72	83–86	225	0.340	0.403	0.384
0.73–0.76	79–82	333	0.349	0.404	0.388
0.77–0.79	76–78	235	0.354	0.401	0.388
0.80–0.82	73–75	285	0.360	0.400	0.390
0.83–0.85	71–72	261	0.366	0.399	0.390
0.86–0.89	67–70	277	0.370	0.395	0.389
0.90–0.96	63–67	301	0.380	0.394	0.391
0.97–1.38	43–62	244	0.391	0.384	0.385

RR, RMSE = 0.0224 and R squared = 0.445 for women). Because of these similarities men and women were pooled for further analyses.

Stepwise regression was used to investigate the simultaneous effects on QT from RR, sex and age and their higher-order interactions, as well as RR^2 to allow for curvature. The single most important variable was the duration of the RR cycle, which explained 42.2% of the QT variance; this was followed by sex which explained an additional 3.6% of the variance. Although age, RR^2, and the interaction term RR · age also were statistically significant (each at $p < 0.005$), their clinical and biologic importance were minimal, because none of these individually accounted for even 1% of the QT variance; all together they accounted for only 1.4% after adjustment for RR and sex. Therefore, we selected the 2-variable linear model: Fitted QT = 0.234 + 0.154 · RR − 0.012 · male. This model yielded an RMSE of 0.0224 and R^2 of 0.458, and was the simplest model that was adequate to predict QT in our combined sample of men and women.

The basic linearity and goodness-of-fit for the QT-RR relation is demonstrated in Figure 1, where each data point represents mean QT versus RR deciles. This plot establishes that the fitted lines adhere closely to the group means with no evidence of gross departure from linearity at any RR value either in men or women.

QT correction: linear versus Bazett: The linearly corrected QT (QT_{LC}), has the same expression for men and women, namely: $QT_{LC} = QT + 0.154 \cdot (1.00 - RR)$ where QT and RR are measured values and 0.154 is the estimated regression slope. A subject with a heart rate >60 beats/min (RR <1) has a QT_{LC} >QT, whereas one with a heart rate <60 beats/min (RR >1) has a QT_{LC} <QT (i.e., the linear correction is upward when the RR interval is shorter than 1 second and downward when it is longer than 1 second).

Mean QT_c and QT_{LC} were computed for each RR decile (Figure 2). The mean QT_{LC} values are virtually constant across the range of RR values. In contrast the QT_c values decline with increasing RR deciles. Thus, the linear correction for QT yields a valid correction;

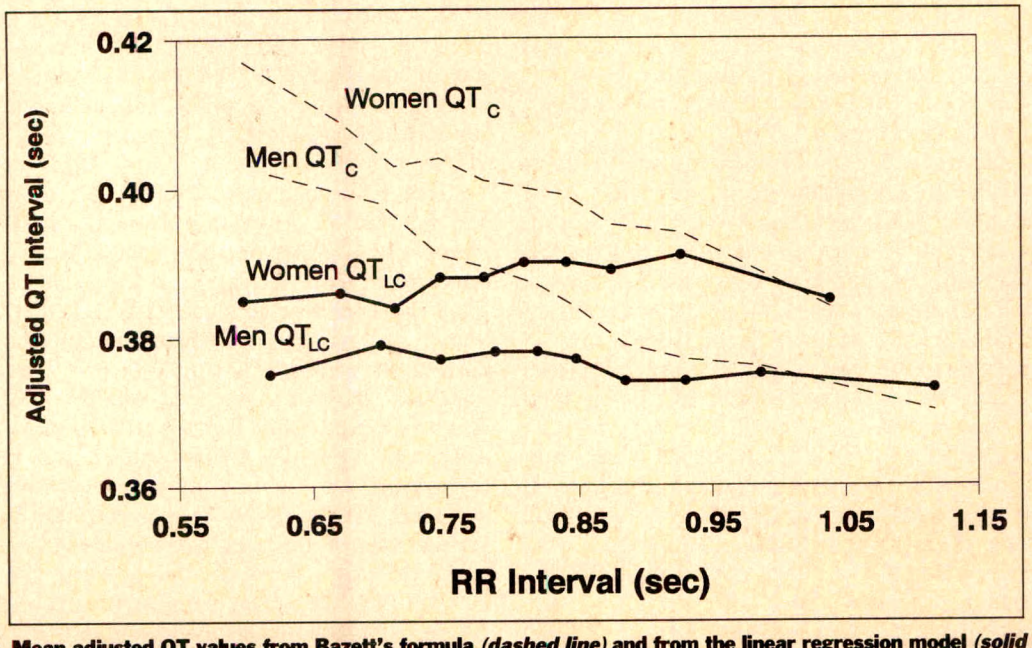


FIGURE 2. Mean adjusted QT values from Bazett's formula *(dashed line)* and from the linear regression model *(solid line)* are plotted for each decile of RR (sec) interval in men and women. Mean QT_{LC} values are virtually constant across the range of RR values for both sexes, whereas Bazett's method provides QT_c values that are not constant over the range of RR intervals.

TABLE IV Mean Predicted QT Values (and lower and upper 95% limits) at Different RR Cycle Lengths

RR (sec)	Heart Rate (beats/min)	QT for Men (sec)			QT for Women (sec)		
		Mean Value	Lower Limit	Upper Limit	Mean Value	Lower Limit	Upper Limit
0.50	120	0.299	0.255	0.343	0.311	0.267	0.354
0.55	109	0.307	0.263	0.351	0.318	0.274	0.362
0.60	100	0.314	0.270	0.358	0.326	0.282	0.370
0.65	92	0.322	0.278	0.366	0.334	0.290	0.378
0.70	86	0.330	0.286	0.374	0.341	0.297	0.385
0.75	80	0.337	0.293	0.381	0.349	0.305	0.393
0.80	75	0.345	0.301	0.389	0.357	0.313	0.401
0.85	71	0.353	0.309	0.397	0.364	0.321	0.408
0.90	67	0.361	0.317	0.404	0.372	0.328	0.416
0.95	63	0.368	0.324	0.412	0.380	0.336	0.424
1.00	60	0.376	0.332	0.420	0.388	0.344	0.432
1.05	57	0.384	0.340	0.428	0.395	0.351	0.439
1.10	55	0.391	0.347	0.435	0.403	0.359	0.447
1.15	52	0.399	0.355	0.443	0.411	0.367	0.455
1.20	50	0.407	0.363	0.451	0.418	0.374	0.462
1.25	48	0.414	0.370	0.458	0.426	0.382	0.470
1.30	46	0.422	0.378	0.466	0.434	0.390	0.478
1.35	44	0.430	0.386	0.474	0.441	0.397	0.486
1.40	43	0.438	0.394	0.482	0.449	0.405	0.493
1.45	41	0.445	0.401	0.489	0.457	0.413	0.501
1.50	40	0.453	0.409	0.497	0.465	0.421	0.509

the group mean QT_{LC} values were between 0.373 and 0.379 for men, and between 0.384 and 0.391 for women. Small sex differences in QT_{LC} were observed with mean values of 0.376 in men and 0.388 in women. Because of the large sample size, limits for the central 95% of individual QT_{LC} values are approximated by the expression QT_{LC} (mean) ± 1.96 · RMSE. These 95% limits for QT_{LC} are 0.332 to 0.420 for a man and 0.344 to 0.432 for a woman. A subject whose QT_{LC} is outside these sex-specific limits is considered to have an unusually short (or long) QT interval. Lower and upper limits of the QT_c distribution are not constant over the observed range of RR, but must be determined anew at each RR value. The impact of different deciles of RR intervals on QT, QT_c and QT_{LC} in men and women is presented in Tables II and III.

Bazett's formula, $QT_c = QT/\sqrt{RR}$, also adjusts upward when RR is <1, and downward when RR is >1 second. But, it yields substantial overadjustment at short RR intervals and underadjustment at long RR intervals (Figure 2). Bazett's "correction" is flawed, whereas the linear adjustment QT_{lc} produces a common reference value for all members of the same sex.

Another way to use the linear model for clinical purposes is to construct 95% confidence limits for an individual QT observation at different RR cycle lengths. These data are listed in Table IV. A subject whose measured QT falls outside the appropriate limits has an unusually short (or long) duration QT interval. This table alleviates the need to compute QT_{LC}, although it may require linear interpolation when a measured RR lies between tabulated values.

DISCUSSION

Assessment of a heart rate–adjusted QT interval is considered to be clinically important, since prolongation of this interval is associated with increased incidence of malignant ventricular arrhythmias and sudden death.[1–12] To use heart rate–corrected QT to predict life-threatening arrhythmias and sudden death, it would be appropriate to use a QT correction formula that is developed and validated in a large population-based cohort. Using Framingham Heart Study subjects, we developed a linear regression equation (QT_{LC}) that more accurately corrects QT for heart rate than the traditionally used Bazett's (QT_c) formula. We found that QT_c undercorrects QT at slow heart rates and overcorrects it at fast heart rates, whereas QT_{LC} reliably corrects QT across a wide range of RR cycle lengths. The large number of subjects studied also enabled us to subdivide the sample into deciles of RR intervals and to examine the impact of different cycle lengths on QT, QT_c and QT_{LC}.

Several formulas have been proposed to adjust the QT interval for heart rate.[13–22] The most frequently used is Bazett's square root formula which was introduced more than 70 years ago.[13] However, the adequacy of this nonlinear formula, obtained from data on 39 young men, has been questioned because the QT_c overcorrects the measured QT interval at fast heart rate and undercorrects it at a low heart rate.[16–22] Our data confirm this deficiency of Bazett's correction. Puddu et al[17] examined 10 mathematically different QT prediction formulas in 881 middle-aged men and provided similar evidence that the QT is overcorrected by Bazett's formula at high heart rates. They observed that the cubed root Fridericia's formula[20] fitted the data better than Bazett's or other formulas. In the present study we tested the regression models used by Puddu and found that most of them (except Bazett's formula) adequately and equally fitted the QT-RR data. Our results generally agree with those of Puddu,[17] but we included women as

well as men, and we did not make arbitrary distinctions between several models that fit equally well.

Since the adequacy of the linear regression model was not inferior to the others, it was chosen as the most suitable simple equation that could be used conveniently in clinical practice. With use of this formula, there is no need for further adjustment using a secondary correcting nomogram as one does with Bazett's formula. Alternatively, a table of lower and upper limits of QT interval for different RR cycles (Table IV) can be used by clinicians for references purposes. This approach obviates the need for using any QT correction formula (QT_c or QT_{LC}). The reliability of this model results from its derivation in a large population-based sample. The same formula applies for men and women (owing to the almost identical linear regression slope).

One limitation of the present study is that QT measurements were collected from resting electrocardiograms. We did not have the option to test whether our linear model applies at extreme values of heart rate. Also, the regression model accounts for <50% of the variance of the QT interval. This indicates that the QT interval is related not only to heart rate, but also to several other factors such as changes in autonomic neural tone and metabolic factors.[25–28] It is clear that individual variability is large.

Controversy persists regarding the significance of QT prolongation as a risk factor for sudden cardiac death in healthy subjects[29–31] and in patients after myocardial infarction.[8–12] Each of these earlier studies used Bazett's formula to adjust QT for heart rate and applied the same value for QT_c prolongation of 440 ms as the upper limit of normal. Additional research is warranted to determine if linear correction of the QT interval improves our ability to detect patients at risk for malignant ventricular arrhythmias and sudden death.

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Reversal of Human Platelet Aggregation by Low Concentrations of Nitroglycerin In Vitro in Normal Subjects

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The potential reversal of platelet aggregation in vitro by nitroglycerin in low concentrations was explored using both optical aggregometry and electron microscopy. Venous blood was collected from a cohort of normal volunteers (20 men and 10 women) aged 21 to 65 years. Aggregation in platelet-rich plasma was induced by adenosine diphosphate in concentrations just sufficient to maintain a steady state of aggregation, without a spontaneous disaggregation phase (3.5 to 5 μM). Administration of nitroglycerin after the induction of aggregation caused both inhibition of the primary wave of developing aggregation and marked disaggregation. This combined effect was maximal when nitroglycerin was added at 0.5 minute after the beginning of aggregation. The observed reversal of platelet aggregation by nitroglycerin was concentration-dependent. Significant effects occurred with nitroglycerin concentrations $\geq 10^{-8}$ M. Concentration associated with 50% reversal of aggregation was 1.52 ± 0.24 (SEM) $\times 10^{-6}$ M. Electron microscopy revealed that 10^{-6} M nitroglycerin induced a significant reduction in both platelet clumping and morphologic changes associated with aggregation. The results of the current study suggest a beneficial antiplatelet effect of nitroglycerin in restoring homeostasis in the face of incipient platelet aggregation. The clinical use of nitroglycerin in patients with acute ischemic syndromes may rest on this action.

(Am J Cardiol 1992;70:802–806)

Effects of nitroglycerin and related organic nitrates on platelet aggregation have been studied extensively, but remain controversial. Whereas in vivo[1,2] and ex vivo[3–5] studies reveal apparent antiplatelet efficacy of nitrates in ordinary clinical doses, inhibition of platelet aggregation in vitro occurred only at supra-pharmacologic concentrations.[6–10] The basis for this paradox merits further examination. The physiologic action of nitrates is related to their thiol-mediated bioconversion to nitric oxide, and interaction of the latter with soluble guanylate cyclase.[11–13] In platelets, this enzyme mediates the antiplatelet effects of nitric oxide donors.[10,12,14,15] Recently we have observed[15] a transient increase in platelet guanylate cyclase responsiveness to sodium nitroprusside during aggregation, which facilitated the disaggregating effect of nitroprusside. It therefore seemed possible that administration of nitroglycerin to platelets after the induction of aggregation might increase the manifestation of its antiplatelet effects. In the current study we explored potential reversal of adenosine diphosphate-induced platelet aggregation by nitroglycerin in low concentrations, using both optical aggregometry and electron microscopy.

METHODS

Subjects: A cohort of 30 normal volunteers (20 men and 10 women aged 40 ± 4 [mean ± SEM] years [range 21 to 65]) was studied, using venesection from an antecubital vein. No subject had taken either cyclooxygenase inhibitors or nitrates for 2 weeks before the study. The protocol was approved by the ethics of research committee of the Queen Elizabeth Hospital, and informed consent was obtained before study entry.

Preparation of platelets and aggregation studies: Blood samples were collected into 1:10 volume of anticoagulant (2 parts of 0.1 M citric acid to 3 parts of 0.1 M trisodium citrate) and centrifuged at 250 g for 10 minutes at room temperature to obtain platelet-rich plasma. Platelet-poor plasma was prepared by further centrifugation of the remaining blood at 2,500 g for 20 minutes. Platelet counts were performed on the S-plus VI Coulter Counter (Coulter Electronics Inc., USA) and platelet-rich plasma was adjusted with platelet-poor plasma to a constant count of 250,000/μL.

Aggregation was measured at 37°C according to Born's turbidometric method[16] on a 4-channel aggregometer (PAP-4, Bio-Data) at a stirring speed of 1200 rpm. Optical density for platelet-rich and platelet-poor plasma was set at 0 and 100%, respectively. Aggregation was induced by adenosine diphosphate in appropri-

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TABLE I Comparison of Changes in Platelet Morphology and Degree of Aggregation as Assessed by Electron Microscopy

Experiment	Degree of Platelet Interaction		Morphologic Changes	
	ADP	ADP/NTG	ADP	ADP/NTG
1	4.0	1.5	30.0	22.5
2	4.0	1.0	23.5	10.0
3	4.0	3.0	30.0	28.5
4	4.0	0.5	30.0	10.0
5	4.0	1.5	30.0	20.0
6	3.5	1.0	30.0	20.0
Mean ± SEM	3.92 ± 0.08	1.42 ± 0.35	28.92 ± 1.08	18.50 ± 2.97
p value	<0.001		<0.01	

See text for details of scoring methodology.
ADP = adenosine diphosphate; NTG = nitroglycerin.

ate concentrations. Nitroglycerin was added to platelets after the beginning of aggregation, and the reversal of aggregation was evaluated 10 minutes later as a percentage comparing the extents of aggregation in the absence (control) and presence of nitroglycerin.

Nitroglycerin (GTN-Pohl, Fisons, Australia) was diluted from initial ethanol solution (5 mg/ml) with Owren's buffer (pH 7.35) to final nitroglycerin concentrations of 10^{-9} to 2×10^{-4} M. Control studies with matched concentrations of ethanol revealed no effects on platelet aggregation. Because of potential effects of higher concentrations of ethanol on platelet aggregation, all experiments involving final nitroglycerin concentrations $>2 \times 10^{-4}$ M used an aqueous nitroglycerin preparation (Aquo-Trinitrosan, Merck, Germany).

Electron microscopy technique: Studies were performed on platelets from 6 subjects. Platelet samples examined represented (1) baseline state, (2) platelets exposed to adenosine diphosphate within 10 minutes, and (3) platelets to which 1 μM nitroglycerin had been added at 0.5 minute after the induction of aggregation. For primary fixation of platelets, 0.5 ml aliquots of platelet-rich plasma were combined with 9.5 ml of a mixture of 1% glutaraldehyde and 4% formaldehyde in 0.1 M sodium cacodylate buffer, pH 7.3.[17] Fixation was performed for a minimum of 30 minutes, and samples were centrifuged for 5 minutes at 500 g. The centrifuged platelets were finally fixed in 2% osmium tetroxide in 0.1 M sodium cacodylate buffer for 30 minutes. This was followed by en-bloc staining in 2% aqueous uranyl acetate. After dehydration with a graded series of ethanol concentrations, samples were embedded in epoxy resin. Survey sections were cut and stained with toluidine blue. Ultrathin sections were cut on a diamond knife and then stained with 2% uranyl acetate and lead citrate. Sections were examined and photographed in a Hitachi H-600 electron microscope. Investigators involved in preparation of electron micrographs were unaware of the individual protocol chosen for the various samples.

Scoring: Electron microscope photographs prepared from 2 representative sections of the fields were examined according to an arbitrarily chosen and prospectively elected scoring analysis scale and performed independently in a double-blind manner by 2 of the investigators. The photographs were assessed at 2 magnifications: ×6,000 and ×18,000.

The lower magnification was used for quantitation of platelet interaction, that is, overall view of relative degree of aggregation. The technique for scoring the extent of platelet interaction (i.e., clumping and adhesion) involved a range of 0 to 4 points.

The higher magnification was used for assessing morphologic changes of platelet aggregates according to the extent of changes in the following criteria: (1) pseudopodia formation, (2) change from discoid shape, (3) granulation, (4) rearrangement of microtubules, and (5) vacuolation. In scoring morphologic changes related to

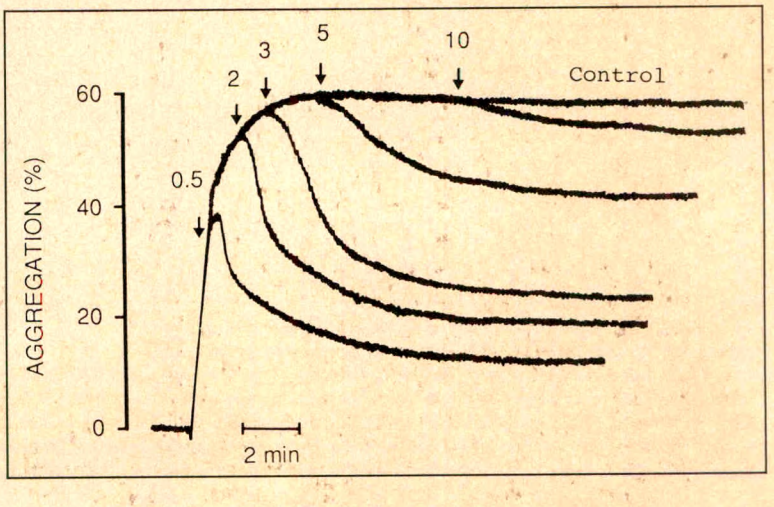


FIGURE 1. Effects of nitroglycerin, administered at different times, on adenosine diphosphate-induced aggregation in platelet-rich plasma. *Arrows* indicate the time (minutes) of addition of 0.1 mM nitroglycerin after the induction of aggregation by 5 μM adenosine diphosphate. The depicted experiment was typical of 5 others.

each of the above 5 criteria, a prospectively derived scale representing graded degree of the transition between morphology of resting platelets and those of fully aggregated platelets was used, based on random examination of 2 regions of each slide. The scoring range of 0 (resting platelets) to 6 points (maximal involvement) was used for each criterion, yielding a maximal cumulative score of 30 points for morphologic criteria.

Data analysis: Statistical assessment of individual points on the concentration-response curve was performed using Dunnett's *t* test for multiple comparisons. Comparisons of drug concentrations inducing 50% effect were made with 2-tailed nonpaired Student's *t* test. Comparison of extent of changes in platelet morphology and clumping on electron microscopic examination was made utilizing the paired *t* test. A statistically significant difference was limited to $p < 0.05$. Results are expressed as mean ± SEM.

RESULTS

To examine possible nitroglycerin-induced reversal of platelet aggregation, we used adenosine diphosphate in concentrations just sufficient to maintain a steady state of aggregation, without a spontaneous disaggregation phase, within the time of experiment. This concentration, normally 3.5 to 5 μM, was evaluated in each experiment and depended on the aggregability of the platelets used.

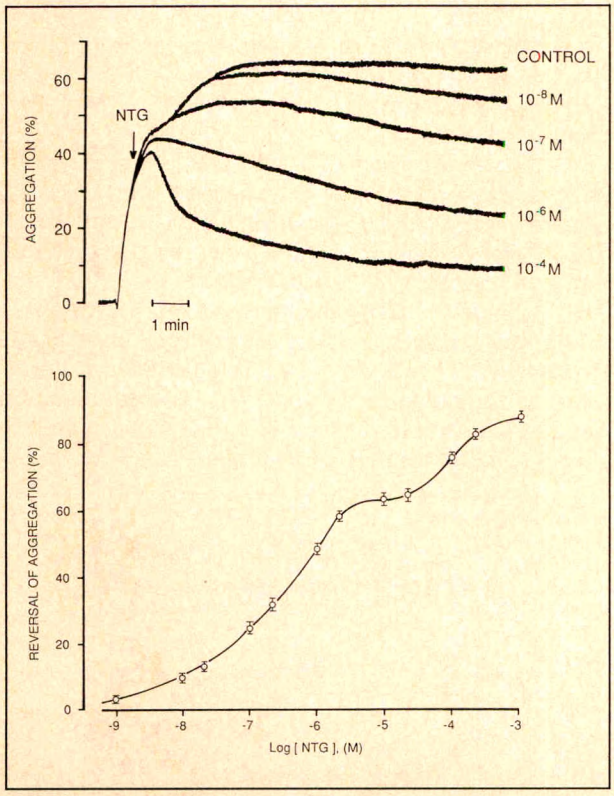


FIGURE 2. Reversal of adenosine diphosphate-induced aggregation by nitroglycerin (NTG). Typical aggregograms *(top)* and concentration-response curve *(bottom)*. Nitroglycerin was administered at 0.5 minute after the induction of aggregation. Concentrations of nitroglycerin are indicated adjacent to the appropriate aggregograms. The concentration-response *curve* represents data from 20 independent experiments (men).

When nitroglycerin was administered after the induction of aggregation, it caused disaggregation (Figure 1). The rate and extent of disaggregation varied according to the time of nitroglycerin administration. The maximal disaggregating rate was observed when nitroglycerin was added to platelets 3 minutes after the beginning of aggregation. If nitroglycerin was adminis-

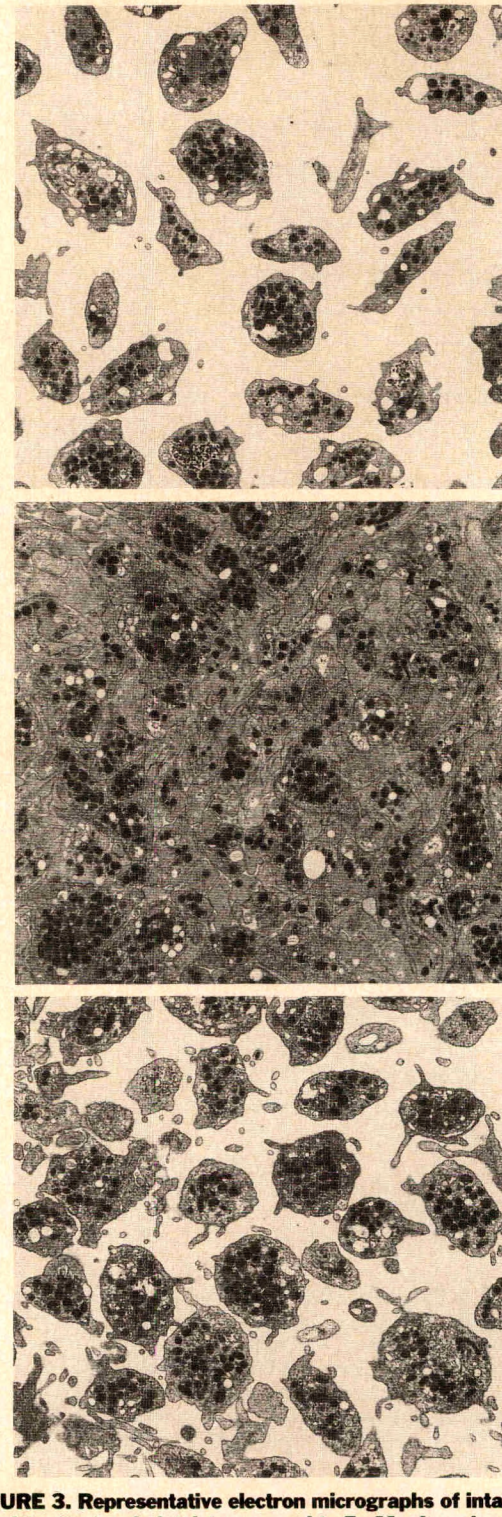


FIGURE 3. Representative electron micrographs of intact platelets *(top)* and platelets exposed to 5 μM adenosine diphosphate for 10 minutes without *(middle)* or with *(bottom)* 10^{-6} M nitroglycerin, administered at 0.5 minute after the induction of aggregation. Magnification ×4,300.

tered earlier, it induced both inhibition of aggregation and marked disaggregation. This combined effect was maximal when nitroglycerin was added at 0.5 minute after induction of aggregation. The observed reversal of platelet aggregation by nitroglycerin was concentration-dependent (Figure 2). Significant effects occurred with concentrations of $\geq 10^{-8}$ M. The concentration of nitroglycerin associated with 50% reversal of aggregation (C_{50}) was $1.52 \pm 0.24 \times 10^{-6}$ M. Although platelets from women exhibited increased sensitivity to adenosine diphosphate compared with those from men (concentrations of adenosine diphosphate inducing 50% aggregation were 2.19 ± 0.22 and 3.26 ± 0.20 μM for women and men, respectively; $p < 0.01$) (consistent with previous results[7]), platelet responses to the disaggregating action of nitroglycerin did not vary between sexes (the values of C_{50} were 1.49 ± 0.28 and $1.58 \pm 0.51 \times 10^{-6}$ M for men and women, respectively).

The results of examination of electron micrographs are summarized in Table I, and representative fields shown in Figure 3. On the basis of the scoring criteria used (see Methods), 10^{-6} M nitroglycerin induced a significant reduction in both extent of interplatelet interaction ("clumping") ($p < 0.001$) and of morphologic changes ($p < 0.01$). Nitroglycerin appeared to reduce the extent of each of the morphologic changes associated with platelet aggregation.

DISCUSSION

The results of the current study delineate the disaggregating action of nitroglycerin in vitro using both optical aggregometry and electron microscopy. Platelet disaggregation, which (like inhibition of aggregation) has been documented previously only with high concentrations of nitroglycerin,[18] was shown to occur with nitroglycerin concentrations as low as 10^{-8} M in the current study, with C_{50} values of approximately 10^{-6} M (Figure 2). Furthermore, electron microscopy confirmed that this concentration of nitroglycerin was sufficient to induce marked limitation of both platelet aggregation and associated morphologic changes compared with platelets affected by adenosine diphosphate alone (Table I; Figure 3). Thus, antiplatelet effects of nitroglycerin are seen with concentrations achievable during therapeutic use of the drug.

The basis for detecting reversal of platelet aggregation with low concentrations of nitroglycerin in the current study was the administration of the drug after the induction of aggregation. Inasmuch as platelet sensitivity to the disaggregating effects of nitric oxide donors increases after the initiation of aggregation, due to a temporary elevation in platelet guanylate cyclase reactivity to nitric oxide,[15] a corresponding peak in the dynamics of nitroglycerin-induced reversal of platelet aggregation could be expected to occur. Consistent with these expectations, the most pronounced effects were observed when nitroglycerin was added to platelets 0.5 to 3 minutes after the beginning of aggregation (Figure 1).

Study limitations: Although it is apparent from the results obtained that nitroglycerin in relatively low concentrations exerts significant effects on platelet aggregation and disaggregation, the observed effect of nitroglycerin may represent an underestimate of the extent of changes that would be induced in vivo. The basis for this underestimate may include progressive inactivation of nitroglycerin during the course of the experiment[19] and the absence of such endogenous agents as prostaglandin E_1, prostacyclin and tissue-type plasminogen activator, which potentiate the disaggregating effects of nitric oxide donors.[18,20–22] Whether nitroglycerin would interact to a similar extent with aggregation induced by agents other than adenosine diphosphate remains to be established. Moreover, the implications of disaggregation of platelets on subsequent platelet functions remain important issues for future examination.

Clinical relevance: The model used in the current study — incipient platelet aggregation followed by potential disaggregation — is reminiscent of the early steps leading to thrombus formation in patients with

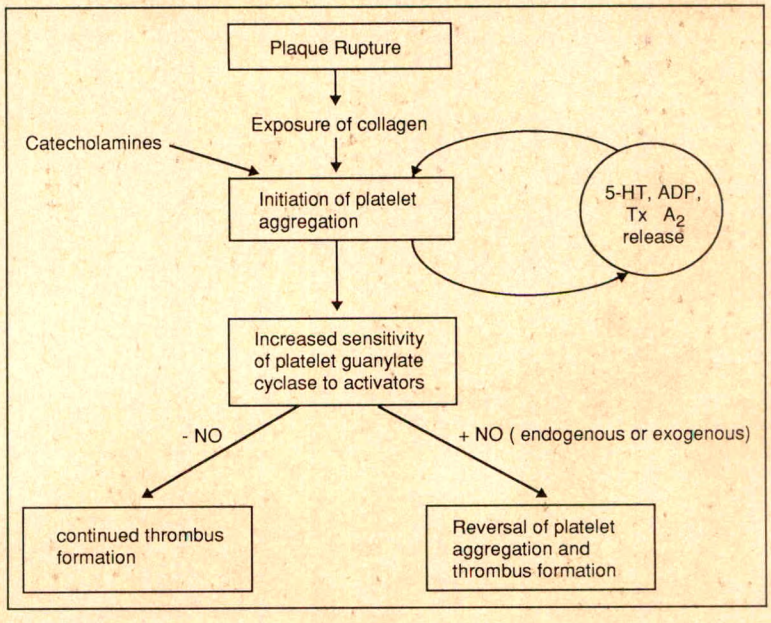


FIGURE 4. Scheme for the potential role of nitroglycerin or other nitric oxide (NO) donors and endogenous nitric oxide in modulating the process of platelet aggregation in acute ischemic syndromes. ADP = adenosine diphosphate; Tx A_2 = thromboxane A_2; 5-HT = 5-hydroxytryptamine, serotonin.

acute ischemic syndromes.[3,23–25] Recent investigations have established that nitroglycerin exerts an important influence on this process in an in vivo model of coronary artery stenosis,[2] and suggest that previously documented beneficial effects of concomitant administration of nitrates and thrombolytic agents[26,27] may reflect changes in thrombus formation as well as vasodilator effects. The results of the current study, by demonstrating the effects of nitroglycerin in reversing platelet aggregation, suggest a beneficial effect of this agent that is maximal once the process of platelet aggregation has been initiated. The basis for this phenomenon could be the increase in platelet guanylate cyclase reactivity to nitric oxide donors induced by the process of aggregation[15]; lack of consideration of this factor in previous in vitro studies[4,7,9,10] contributed to underestimation of the extent of nitroglycerin effects as an antiplatelet agent.

One may postulate that this action of nitroglycerin, an exogenous donor of nitric oxide, would also apply in the case of endogenous activators of guanylate cyclase such as endothelium-derived relaxing factor. The study therefore points to a pivotal role of nitric oxide donors (endogenous or exogenous) in restoring homeostatic mechanisms in the face of incipient platelet aggregation (Figure 4). The clinical use of nitrates in patients with acute ischemic syndromes may rest primarily on this action.

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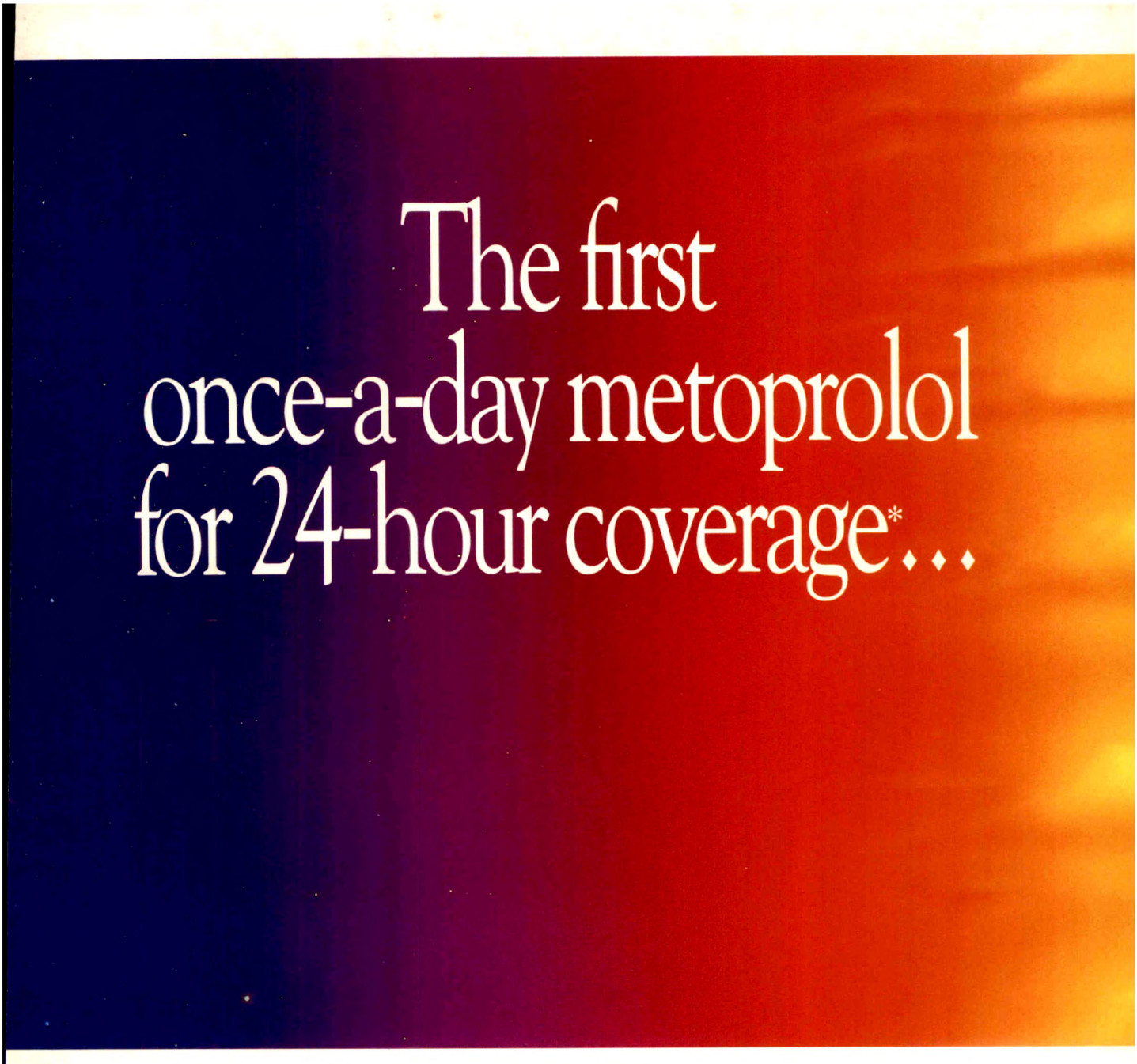
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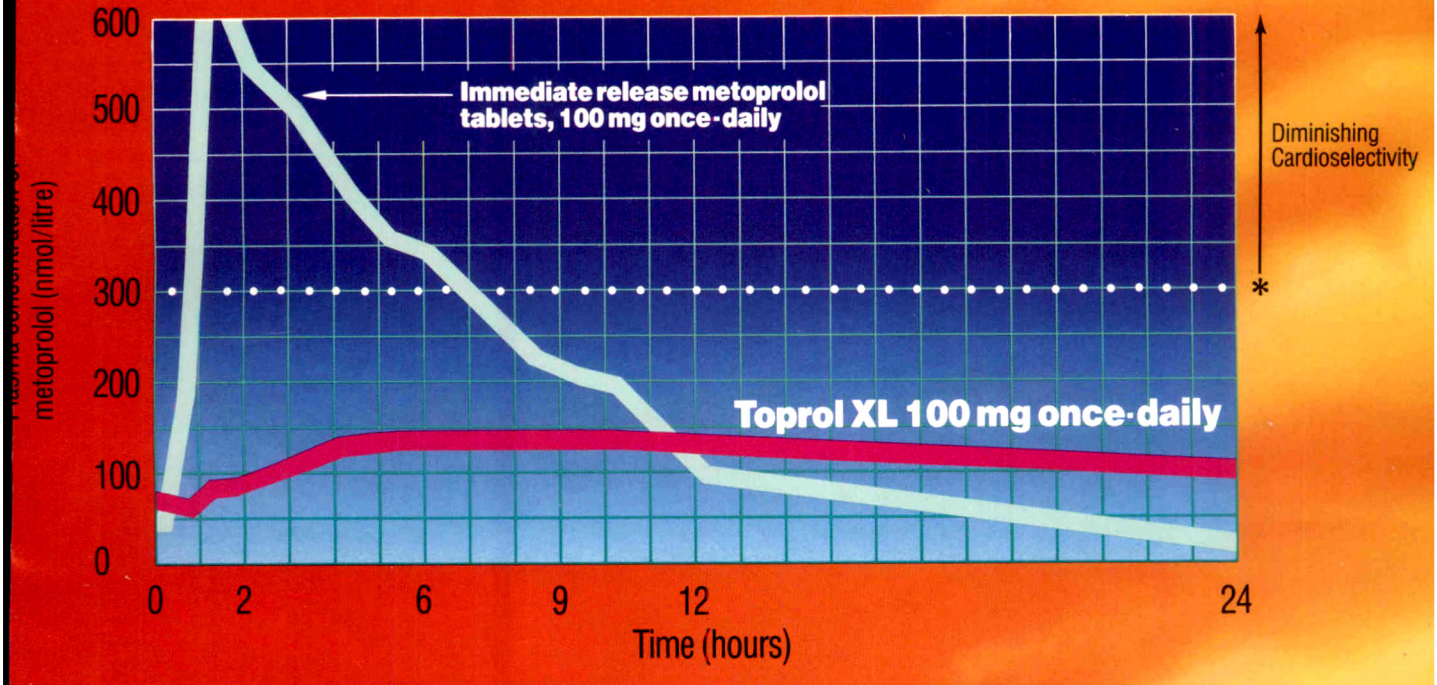


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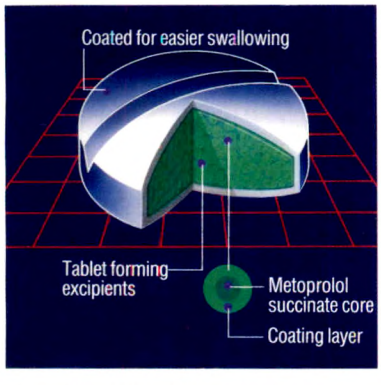
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TOPROL XL for compliance and 24-hour coverage.



Graph reproduced with revisions and permission from Sandberg et al.[2]

* The concentration-effect curve begins reaching a plateau between 200-300 nmol/L, and higher plasma levels produce little additional $beta_1$-blocking effect. The relative $beta_1$-selectivity of metoprolol diminishes and blockade of $beta_2$-adrenoceptors increases at higher plasma concentrations



The TOPROL XL delivery system releases metoprolol at a controlled and predictable rate[1]

- TOPROL XL is a proprietary formulation that provides the benefits of extended release tablets
- TOPROL XL has been used in over 1,000,000 patient-years worldwide[3]

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TOPROL XL™ TABLETS

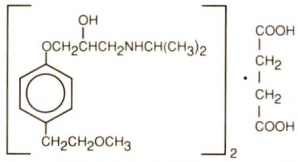
(Metoprolol succinate)

Extended Release Tablets

Tablets: 50 mg, 100 mg, and 200 mg

DESCRIPTION

Toprol XL, metoprolol succinate, is a beta$_1$-selective (cardioselective) adrenoceptor blocking agent, for oral administration, available as extended release tablets. Toprol XL has been formulated to provide a controlled and predictable release of metoprolol for once daily administration. The tablets comprise a multiple unit system containing metoprolol succinate in a multitude of controlled release pellets. Each pellet acts as a separate drug delivery unit and is designed to deliver metoprolol continuously over the dosage interval. The tablets contain 47.5 mg, 95 mg and 190 mg of metoprolol succinate equivalent to 50, 100 and 200 mg of metoprolol tartrate, USP, respectively. Its chemical name is (±)1-(isopropylamino)-3-[p-(2-methoxyethyl) phenoxy]-2-propanol succinate (2:1) (salt). Its structural formula is:



Metoprolol succinate is a white crystalline powder with a molecular weight of 652.8. It is freely soluble in water; soluble in methanol; sparingly soluble in ethanol; slightly soluble in dichloromethane and 2-propanol; practically insoluble in ethyl-acetate, acetone, diethylether and heptane. Inactive ingredients: Silicone dioxide, Cellulose compounds, Acetyltributyl citrate, Maize starch, Lactose powder, Polyvidone, Magnesium stearate, Polyethylene glycol, Titanium dioxide, Paraffin.

CLINICAL PHARMACOLOGY

Metoprolol is a beta$_1$-selective (cardioselective) adrenergic receptor blocking agent. This preferential effect is not absolute, however, and at higher plasma concentrations, metoprolol also inhibits beta$_2$-adrenoreceptors, chiefly located in the bronchial and vascular musculature. Metoprolol has no intrinsic sympathomimetic activity, and membrane-stabilizing activity is detectable only at plasma concentrations much greater than required for beta-blockade. Animal and human experiments indicate that metoprolol slows the sinus rate and decreases AV nodal conduction.

Clinical pharmacology studies have confirmed the beta-blocking activity of metoprolol in man, as shown by (1) reduction in heart rate and cardiac output at rest and upon exercise, (2) reduction of systolic blood pressure upon exercise, (3) inhibition of isoproterenol-induced tachycardia, and (4) reduction of reflex orthostatic tachycardia.

The relative beta$_1$-selectivity of metoprolol has been confirmed by the following: (1) In normal subjects, metoprolol is unable to reverse the beta$_2$-mediated vasodilating effects of epinephrine. This contrasts with the effect of nonselective beta-blockers, which completely reverse the vasodilating effects of epinephrine. (2) In asthmatic patients, metoprolol reduces FEV$_1$ and FVC significantly less than a nonselective beta-blocker, propranolol, at equivalent beta$_1$-receptor blocking doses.

In five controlled studies in normal healthy subjects, the same daily doses of Toprol XL and immediate release metoprolol were compared in terms of the extent and duration of beta$_1$-blockade produced. Both formulations were given in a dose range equivalent to 100–400 mg of immediate release metoprolol per day. In these studies, Toprol XL was administered once a day and immediate release metoprolol was administered once to four times a day. A sixth controlled study compared the beta$_1$-blocking effects of a 50 mg daily dose of the two formulations. In each study, beta$_1$-blockade was expressed as the percent change from baseline, in exercise heart rate following standardized submaximal exercise tolerance tests at steady state. Toprol XL administered once a day, and immediate release metoprolol administered once to four times a day, provided comparable total beta$_1$-blockade over 24 hours (area under the beta$_1$-blockade versus time curve) in the dose range 100-400 mg. At a dosage of 50 mg once daily, Toprol XL produced significantly higher total beta$_1$-blockade over 24 hours than immediate release metoprolol. For Toprol XL, the percent reduction in exercise heart rate was relatively stable throughout the entire dosage interval and the level of beta$_1$-blockade increased with increasing doses from 50 to 300 mg daily. The effects at peak/trough (i.e. at 24 hours post dosing) were; 14/9, 16/10, 24/14, 27/22 and 27/20% reduction in exercise heart rate for doses of 50, 100, 200, 300 and 400 mg Toprol XL once a day, respectively. In contrast to Toprol XL immediate release metoprolol given at a dose of 50–100 mg once a day, produced a significantly larger peak effect on exercise tachycardia, but the effect was not evident at 24 hours. To match the peak to trough ratio obtained with Toprol XL over the dosing range of 200 to 400 mg, a t.i.d. to q.i.d. divided dosing regimen was required for immediate release metoprolol.

The relationship between plasma metoprolol levels and reduction in exercise heart rate is independent of the pharmaceutical formulation. Using the E_{max} model, the maximal beta$_1$-blocking effect has been estimated to produce a 28.3% reduction in exercise heart rate. Beta$_1$-blocking effects in the range of 30–80% of the maximal effect (corresponding to approximately 8–23% reduction in exercise heart rate) are expected to occur at metoprolol plasma concentrations ranging from 30–540 nmol/L. The concentration-effect curve begins reaching a plateau between 200–300 nmol/L, and higher plasma levels produce little additional beta$_1$-blocking effect. The relative beta$_1$-selectivity of metoprolol diminishes and blockade of beta$_2$-adrenoceptors increases at higher plasma concentrations.

Although beta-adrenergic receptor blockade is useful in the treatment of angina and hypertension, there are situations in which sympathetic stimulation is vital. In patients with severely damaged hearts, adequate ventricular function may depend on sympathetic drive. In the presence of AV block, beta-blockade may prevent the necessary facilitating effect of sympathetic activity on conduction. Beta$_2$-adrenergic blockade results in passive bronchial constriction by interfering with endogenous adrenergic bronchodilator activity in patients subject to bronchospasm and may also interfere with exogenous bronchodilators in such patients.

Hypertension

The mechanism of the antihypertensive effects of beta-blocking agents has not been elucidated. However, several possible mechanisms have been proposed: (1) competitive antagonism of catecholamines at peripheral (especially cardiac) adrenergic neuron sites, leading to decreased cardiac output; (2) a central effect leading to reduced sympathetic outflow to the periphery; and (3) suppression of renin activity.

In controlled clinical studies, an immediate release dosage form of metoprolol has been shown to be an effective antihypertensive agent when used alone or as concomitant therapy with thiazide-type diuretics at dosages of 100–450 mg daily. Toprol XL, in dosages of 100 to 400 mg once daily, has been shown to possess comparable β_1-blockade as conventional metoprolol tablets administered two to four times daily. In addition, Toprol XL administered at a dose of 50 mg once daily has been shown to lower blood pressure 24-hours post-dosing in placebo controlled studies. In controlled, comparative, clinical studies, immediate release metoprolol appeared comparable as an antihypertensive agent to propranolol, methyldopa, and thiazide-type diuretics, and affected both supine and standing blood pressure. Because of variable plasma levels attained with a given dose and lack of a consistent relationship of antihypertensive activity to drug plasma concentration, selection of proper dosage requires individual titration.

Angina Pectoris

By blocking catecholamine-induced increases in heart rate, in velocity and extent of myocardial contraction, and in blood pressure, metoprolol reduces the oxygen requirements of the heart at any given level of effort, thus making it useful in the long-term management of angina pectoris. However, in patients with heart failure, beta-adrenergic blockade may increase oxygen requirements by increasing left ventricular fiber length and end-diastolic pressure.

In controlled clinical trials, an immediate release formulation of metoprolol has been shown to be an effective antianginal agent, reducing the number of angina attacks and increasing exercise tolerance. The dosage used in these studies ranged from 100 to 400 mg daily. Toprol XL, in dosages of 100 to 400 mg once daily, has been shown to possess comparable β_1-blockade as conventional metoprolol tablets administered two to four times daily.

Pharmacokinetics

In man, absorption of metoprolol is rapid and complete. Plasma levels following oral administration of conventional metoprolol tablets, however, approximate 50% of levels following intravenous administration, indicating about 50% first-pass metabolism. Metoprolol crosses the blood-brain barrier and has been reported in the CSF in a concentration 78% of the simultaneous plasma concentration.

Plasma levels achieved are highly variable after oral administration. Only a small fraction of the drug (about 12%) is bound to human serum albumin. Elimination is mainly by biotransformation in the liver, and the plasma half-life ranges from approximately 3 to 7 hours. Less than 5% of an oral dose of metoprolol is recovered unchanged in the urine; the rest is excreted by the kidneys as metabolites that appear to have no clinical significance. Following intravenous administration of metoprolol, the urinary recovery of unchanged drug is approximately 10%. The systemic availability and half-life of metoprolol in patients with renal failure do not differ to a clinically significant degree from those in normal subjects. Consequently, no reduction in dosage is usually needed in patients with chronic renal failure.

In comparison to conventional metoprolol, the plasma metoprolol levels following administration of Toprol XL are characterized by lower peaks, longer time to peak and significantly lower peak to trough variation. The peak plasma levels following once daily administration of Toprol XL average one-fourth to one-half the peak plasma levels obtained following a corresponding dose of conventional metoprolol, administered once daily or in divided doses. At steady state the average bioavailability of metoprolol following administration of Toprol XL, across the dosage range of 50 to 400 mg once daily, was 77% relative to the corresponding single or divided doses of conventional metoprolol. Nevertheless, over the 24 hour dosing interval. β_1-blockade is comparable and dose-related (see CLINICAL PHARMACOLOGY). The bioavailability of metoprolol shows a dose-related, although not directly proportional increase with dose and is not significantly affected by food following Toprol XL administration.

INDICATIONS AND USAGE

Hypertension

Toprol XL tablets are indicated for the treatment of hypertension. They may be used alone or in combination with other antihypertensive agents.

Angina Pectoris

Toprol XL tablets are indicated in the long-term treatment of angina pectoris.

CONTRAINDICATIONS

Hypertension and Angina

Toprol XL is contraindicated in sinus bradycardia, heart block greater than first degree, cardiogenic shock, and overt cardiac failure (see WARNINGS).

WARNINGS

Hypertension and Angina

Cardiac Failure: Sympathetic stimulation is a vital component supporting circulatory function in congestive heart failure, and beta-blockade carries the potential hazard of further depressing myocardial contractility and precipitating more severe failure. In hypertensive and angina patients who have congestive heart failure controlled by digitalis and diuretics, Toprol XL should be administered cautiously. Both digitalis and Toprol XL slow AV conduction.

In Patients Without a History of Cardiac Failure: Continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or given a diuretic. The response should be observed closely. If cardiac failure continues, despite adequate digitalization and diuretic therapy, Toprol XL should be withdrawn.

Ischemic Heart Disease: Following abrupt cessation of therapy with certain beta-blocking agents, exacerbations of angina pectoris and, in some cases, myocardial infarction have occurred. When discontinuing chronically administered Toprol XL, particularly in patients with ischemic heart disease, the dosage should be gradually reduced over a period of 1–2 weeks and the patient should be carefully monitored. If angina markedly worsens or acute coronary insufficiency develops, Toprol XL administration should be reinstated promptly, at least temporarily, and other measures appropriate for the management of unstable angina should be taken. Patients should be warned against interruption or discontinuation of therapy without the physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue Toprol XL therapy abruptly even in patients treated only for hypertension.

Bronchospastic Diseases: PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD, IN GENERAL, NOT RECEIVE BETA-BLOCKERS. Because of its relative beta$_1$-selectivity, however, Toprol XL may be used with caution in patients with bronchospastic disease who do not respond to, or cannot tolerate, other antihypertensive treatment. Since beta$_1$-selectivity is not absolute, a beta$_2$-stimulating agent should be administered concomitantly, and the lowest possible dose of Toprol XL should be used (see DOSAGE AND ADMINISTRATION).

Major Surgery: The necessity or desirability of withdrawing beta-blocking therapy prior to major surgery is controversial; the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures.

Toprol XL like other beta-blockers, is a competitive inhibitor of beta-receptor agonists, and its effects can be reversed by administration of such agents, e.g., dobutamine or isoproterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in restarting and maintaining the heart beat has also been reported with beta-blockers.

Diabetes and Hypoglycemia: Toprol XL should be used with caution in diabetic patients if a beta-blocking agent is required. Beta-blockers may mask tachycardia occurring with hypoglycemia, but other manifestations such as dizziness and sweating may not be significantly affected.

Thyrotoxicosis: Beta-adrenergic blockade may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. Patients suspected of developing thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of beta-blockade, which might precipitate a thyroid storm.

PRECAUTIONS

General

Toprol XL should be used with caution in patients with impaired hepatic function.

Information for Patients

Patients should be advised to take Toprol XL regularly and continuously, as directed, preferably with or immediately following meals. If a dose should be missed, the patient should take only the next scheduled dose (without doubling it). Patients should not discontinue Toprol XL without consulting the physician.

Patients should be advised (1) to avoid operating automobiles and machinery or engaging in other tasks requiring alertness until the patient's response to therapy with Toprol XL has been determined; (2) to contact the physician if any difficulty in breathing occurs; (3) to inform the physician or dentist before any type of surgery that he or she is taking Toprol XL.

Laboratory Tests

Clinical laboratory findings may include elevated levels of serum transaminase, alkaline phosphatase, and lactate dehydrogenase.

Drug Interactions

Catecholamine-depleting drugs (e.g., reserpine) may have an additive effect when given with beta-blocking agents. Patients treated with Toprol XL plus a catecholamine depletor should therefore be closely observed for evidence of hypotension or marked bradycardia, which may produce vertigo, syncope, or postural hypotension.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies in animals have been conducted to evaluate the carcinogenic potential of metoprolol tartrate. In 2-year studies in rats at three oral dosage levels of up to 800 mg/kg/day, there was no increase in the development of spontaneously occurring benign or malignant neoplasms of any type. The only histologic changes that appeared to be drug related were an increased incidence of generally mild focal accumulation of foamy macrophages in pulmonary alveoli and a slight increase in biliary hyperplasia. In a 21-month study in Swiss albino mice at three oral dosage levels of up to 750 mg/kg/day, benign lung tumors (small adenomas) occurred more frequently in female mice receiving the highest dose than in untreated control animals. There was no increase in malignant or total (benign plus malignant) lung tumors, nor in the overall incidence of tumors or malignant tumors. This 21-month study was repeated in CD-1 mice, and no statistically or biologically significant differences were observed between treated and control mice of either sex for any type of tumor.

All mutagenicity tests performed on metoprolol tartrate (a dominant lethal study in mice, chromosome studies in somatic cells, a Salmonella/mammalian-microsome mutagenicity test, and a nucleus anomaly test in somatic interphase nuclei) and metoprolol succinate (a Salmonella/mammalian-microsome mutagenicity test) were negative.

No evidence of impaired fertility due to metoprolol tartrate was observed in a study performed in rats at doses up to 55.5 times the maximum daily human dose of 450 mg.

Pregnancy Category C

Metoprolol tartrate has been shown to increase post-implantation loss and decrease neonatal survival in rats at doses up to 55.5 times the maximum daily human dose of 450 mg. Distribution studies in mice confirm exposure of the fetus when metoprolol tartrate is administered to the pregnant animal. These studies have revealed no evidence of impaired fertility or teratogenicity. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers

Metoprolol is excreted in breast milk in very small quantities. An infant consuming 1 liter of breast milk daily would receive a dose of less than 1 mg of the drug. Caution should be exercised when Toprol XL is administered to a nursing woman.

Pediatric Use

Safety and effectiveness in children have not been established.

Risk Of Anaphylactic Reactions

While taking beta-blockers, patients with a history of severe anaphylactic reactions to a variety of allergens may be more reactive to repeated challenge, either accidental, diagnostic or therapeutic. Such patients may be unresponsive to the usual doses of epinephrine used to treat allergic reaction.

ADVERSE REACTIONS

Hypertension and Angina

Most adverse effects have been mild and transient. The following adverse react
been reported for metoprolol tartrate.

Central Nervous System: Tiredness and dizziness have occurred in about
patients. Depression has been reported in about 5 of 100 patients. Mental conf
short-term memory loss have been reported. Headache, somnolence, nightm
insomnia have also been reported.

Cardiovascular: Shortness of breath and bradycardia have occurred in approxim
100 patients. Cold extremities; arterial insufficiency, usually of the Raynaud typ
tions; congestive heart failure; peripheral edema; syncope; chest pain; and hy
have been reported in about 1 of 100 patients (see CONTRAINDICATIONS, W
and PRECAUTIONS).

Respiratory: Wheezing (bronchospasm) and dyspnea have been reported in a
100 patients (see WARNINGS).

Gastrointestinal: Diarrhea has occurred in about 5 of 100 patients. Nausea, d
gastric pain, constipation, flatulence, digestive tract disorders and heartburn h
reported in about 1 of 100 patients.

Hypersensitive Reactions: Pruritus or rash have occurred in about 5 of 100
Worsening of psoriasis has also been reported.

Miscellaneous: Peyronie's disease has been reported in fewer than 1 of 100,00
Musculoskeletal pain, blurred vision, decreased libido and tinnitus have also been
There have been rare reports of reversible alopecia, agranulocytosis, and
Discontinuation of the drug should be considered if any such reaction is not otherw
cable. The oculomucocutaneous syndrome associated with the beta-blocker pra
not been reported with metoprolol.

Potential Adverse Reactions

A variety of adverse reactions not listed above have been reported with other beta
gic blocking agents and should be considered potential adverse reactions to Toprc

Central Nervous System: Reversible mental depression progressing to cata
acute reversible syndrome characterized by disorientation for time and place,
memory loss, emotional lability, slightly clouded sensorium, and decreased perfor
neuropsychometrics.

Cardiovascular: Intensification of AV block (see CONTRAINDICATIONS).

Hematologic: Agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic

Hypersensitive Reactions: Fever combined with aching and sore throat, laryn
and respiratory distress.

OVERDOSAGE

Acute Toxicity

No overdosage has been reported with Toprol XL and no specific overdosage in
was obtained with this drug, with the exception of animal toxicology data. Howe
Toprol XL (metoprolol succinate salt) contains the same active moiety, metoprolo
ventional metoprolol tablets (metoprolol tartrate salt), the recommendations on ov
for metoprolol conventional tablets are applicable to Toprol XL.

Signs and Symptoms

Potential signs and symptoms associated with overdosage with metoprolol are bra
hypotension, bronchospasm, and cardiac failure.

Treatment

There is no specific antidote.

In general, patients with acute or recent myocardial infarction may be more hem
cally unstable than other patients and should be treated accordingly. On the ba
pharmacologic actions of metoprolol tartrate, the following general measures s
employed.

Elimination of the Drug: Gastric lavage should be performed.

Bradycardia: Atropine should be administered. If there is no response to vagal b
isoproterenol should be administered cautiously.

Hypotension: A vasopressor should be administered, e.g., levarterenol or dopami

Bronchospasm: A beta$_2$-stimulating agent and/or a theophylline derivative s
administered.

Cardiac Failure: A digitalis glycoside and diuretics should be administered. In sho
ing from inadequate cardiac contractility, administration of dobutamine, isoprot
glucagon may be considered.

DOSAGE AND ADMINISTRATION

Toprol XL is an extended release tablet intended for once-a-day administratio
switching from immediate release metoprolol tablet to Toprol XL, the same total d
of Toprol XL should be used.

As with immediate release metoprolol, dosages of Toprol XL should be individua
titration may be needed in some patients.

Toprol XL tablets are scored and can be divided; however, the whole or half tabl
be swallowed whole and not chewed or crushed.

Hypertension

The usual initial dosage is 50 to 100 mg daily in a single dose, whether used
added to a diuretic. The dosage may be increased at weekly (or longer) intervals
mum blood pressure reduction is achieved. In general, the maximum effect of a
dosage level will be apparent after 1 week of therapy. Dosages above 400 mg per
not been studied.

Angina Pectoris

The dosage of Toprol XL should be individualized. The usual initial dosage is 100
given in a single dose. The dosage may be gradually increased at weekly
until optimum clinical response has been obtained or there is a pronounced slowi
heart rate. Dosages above 400 mg per day have not been studied. If treatment is t
continued, the dosage should be reduced gradually over a period of 1–2 we
WARNINGS).

HOW SUPPLIED

Tablets 50 mg:
Contain 47.5 mg of metoprolol succinate equivalent to 50 mg of metoprolol tartrate,
Are white, biconvex, round, film-coated
Engraved $\frac{A}{mo}$ on one side and scored on the other

Bottles of 100 NDC 0186-1090-05

Tablets 100 mg:
Contain 95 mg of metoprolol succinate equivalent to 100 mg of metoprolol tartrate,
Are white, biconvex, round, film-coated
Engraved $\frac{A}{ms}$ on one side and scored on the other

Bottles of 100 NDC 0186-1092-05

Tablets 200 mg:
Contain 190 mg of metoprolol succinate equivalent to 200 mg of metoprolol tartrate
Are white, biconvex, oval, film-coated
Engraved $\frac{A}{my}$ and scored on one side

Bottles of 100 NDC 0186-1094-05

Store at controlled room temperature 15°–30°C (59°–86°F).

Manufactured by:

Astra Pharmaceutical Production, AB
Södertälje, Sweden

Manufactured for:

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Westborough, MA 01581

FOOTNOTES:

1. Please see full prescribing information above.
2. Sandberg A, Blomqvist I, Jonsson UE, Lundborg P. Pharmacokinetic and pharmacodynamic properties of a new controlled-release formulation of metoprolol; a comparisc withconventional tablets. Eur J Clin Pharmacol 1988; 33 (Suppl): S9-S14.
3. Data on file at AB Hassle.

The Prognostic Significance of Ventricular Ectopic Activity

John B. Kostis, MD

The report by Fleg and Kennedy[1] on the long-term prognostic significance of ambulatory electrocardiographic findings in apparently healthy older subjects highlights a continued interest on the risk imposed by the presence of nonsustained and usually asymptomatic ventricular ectopic activity (VEA). In 98 apparently healthy volunteers aged 60 to 85 years from the Baltimore Longitudinal Study of Aging who were followed for 10 years, a relation of ST depression ("silent ischemia") on ambulatory electrocardiography with future coronary events was noted. However, neither ventricular nor atrial ectopic activity were good predictors of coronary events.[1] The relation of intermittent pulse irregularity with prognosis has been noticed since ancient times. Around 600 B.C. the Chinese physician Pien Chio apparently taught that occasional intermittence of the pulse was compatible with normal lifespan, whereas frequent irregularity (i.e., 1 in 10 beats, corresponding to approximately 500 ventricular ectopic complexes [VECs] per hour) implied ominous prognosis (i.e., death within 1 year).[2]

VEA is observed in patients with cardiac disease (usually coronary artery disease, especially recent or old myocardial infarction), and in patients with extracardiac disease (e.g., pulmonary disease) as well as in normal subjects (both subjects without clinical manifestation of disease and subjects in whom cardiac disease has been excluded by diligent noninvasive and invasive testing).[3–6] In apparently normal subjects for whom cardiac disease has not been excluded by extensive testing, VEA is related to evidence of disease or to risk factors of coronary artery disease.[3,7] In all populations, including those with normal coronary arteriograms, VEA increases with age.[6–9] VEA may be related to future risk in 3 ways: (1) as a marker of the presence of cardiac (and extracardiac) disease; (2) as a marker of severity of known cardiac disease; and (3) by increasing risk independently of other measures of disease presence or disease severity (a mechanism implying causality and exemplified by the R on T phenomenon). Kennedy et al[10] reported that frequent and complex VEA on ambulatory electrocardiography was not associated with an adverse outcome in a group of 73 apparently healthy subjects. However, in larger studies of apparently normal subjects, VEA was associated with an increase in risk of future mortality, especially sudden death mortality.[11–14] For example, in a 7.5-year prospective study of 15,637 apparently healthy white men aged 35 to 57 years who were screened for participation in the Multiple Risk Factor Intervention Trial, a relation of the presence, frequency and complexity of VEA on a 2-minute rhythm strip with the risk of sudden death was noted.[14] The increase in risk was attenuated in older persons. A possible explanation for this attenuation of the VEC-risk relation with age is the increased prevalence of ventricular premature complexes with "normal aging," which would lower the specificity of ventricular premature complexes as markers of undetected disease. This phenomenon may also be one explanation for the low predictive value of VEA in the study of Fleg and Kennedy[1] reported in this issue. Other explanations are the low statistical power of the study, and the use of the occurrence of either angina or myocardial infarction or death as the outcome. Since significant ST depression is most often due to ischemia, it is not surprising that it predicts the development of angina and myocardial infarction. This has also been shown for ST depression observed during exercise testing. On the other hand, VEA may have many causes and may also be seen in normal subjects, factors that would be expected to attenuate its relation to risk.

In patients with known coronary artery disease (particularly patients who have survived an acute myocardial infarction), VEA is related to the degree of left ventricular involvement, to residual ischemia, to the extent of coronary arterial narrowing, the age of the infarction, age of the patient and other factors.[15–20] Since these correlates of VEA, especially left ventricular dysfunction and the extent of coronary arterial disease are important determinants of prognosis in these patients, a relation of VEA to mortality should be expected and has been reported by many investigators.[15,16,18,21] This relation is observed in low- and high-risk patient subsets, in patients taking β blockers or antiarrhythmic drugs, in patients who had thrombolytic therapy and those with very low VEC frequency.[18,22–25] In the Beta Blockers Heart Attack Trial, patients with 1 to 12 VECs/day had 50% excess risk compared with those who had no VECs at all during the 24-hour recording.[25] In the Cardiac Arrhythmia Suppression Trial (CAST), a relation of VEA and mortality/resuscitated cardiac arrest was observed in the active treatment group. In the placebo group, there were only 26 events and a relation was not observed.[23]

Different dichotomous definitions of VEA are associated with mortality with similar odds ratios, and a reciprocal relation of sensitivity and specificity of different definitions of VEA in predicting mortality exists.[18] For example, having any VEC per 24 hours is associated with an odds ratio for mortality of 2.32 compared with those who have no VECs, with a sensitivity in predicting

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mortality of 92% and a very low specificity of 17%. Having ≥10 or more VECs/hour is associated with a similar odds ratio (2.69) compared with patients who have <10 VECs/hour, but carries lower sensitivity (26%) and much improved specificity (89%).

In most large studies, the relation of VEA to mortality is independent of other factors (such as left ventricular function, age, and so forth) affecting prognosis. However, coronary disease severity was not considered in most of these trials, raising the possibility that the "independent" contribution of VEA in predicting risk may be because they are markers of more severe coronary arterial involvement. In addition, VEA is associated with both sudden and nonsudden death, implying an association of VEA with disease severity rather than a causal relation of VEA to risk. Finally, demonstration of independent statistical association does not prove causality. The findings of the CAST cast doubt on the causal importance of VEB in increasing risk.[26] In CAST, control of VEA by encainide and flecainide was associated with increased mortality, whereas mortality with moricizine was not significantly different from placebo. Data on a beneficial effect with the use of amiodarone are promising but not yet convincing.[27,28] The outcome of studies now in progress may clarify the role of this agent in reducing mortality, but not the role of antiarrhythmic therapy in general, since amiodarone is also a vasodilator. In the interim, we should keep in mind that VEA is associated with increased risk either as a marker of the presence or severity of disease or as an independent factor. To paraphrase Joseph Stein's Tevye, it is not terrible to have VEA, but it is not a great honor either.

I apologize to the hundreds of investigators who have published on these issues because I could not quote all pertinent references.

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Fascicular Blocks: Not Interpretable from the Electrocardiogram

David H. Spodick, MD, DSc

Introduction of the concept of hemiblock of the left bundle branch system[1] (less erroneously termed "fascicular block") was a pioneering effort that enabled electrocardiographers to think clinically in terms of the pathophysiology of conduction system lesions. Few would dispute that blocks can exist in particular parts of the conduction system, with or without accompanying myocardial lesions. However, it is questionable that one can securely deduce from the ordinary electrocardiogram the presence of such specific forms of interrupted conduction and highly questionable that their anatomic locations can be predicted. Much evidence now exists that the left bundle system only rarely approaches being bifascicular[2,3] (negating any idea of hemiblock, which implies a bifascicular system); although an effective septal ramus can be demonstrated,[4] even a trifascicular system remains too simplistic when dissections of the left bundle system consistently show broader and narrower portions connected by loops and bridges, almost always among an assortment of fan-like smaller fascicles.[2-5] These complex arrangements are further confounded by great intersubject variability.[2,4] Moreover, fine dissection limited to the left bundle conducting system in patients whose electrocardiograms show either left- or right-axis deviation — necessary to even consider a fascicular block from the electrocardiogram — disclose a plethora of lesions, most quite proximal to the proposed anterior and posterior major fascicles.[2,4] Furthermore, many patients with appropriate axis deviations have additional or isolated lesions of the myocardium both adjacent to and remote from the bundle system.[4,6] Long ago, for example, Grant[6] showed that a myocardial lesion in an appropriate location could slow intramyocardial conduction so that the terminal portion of the QRS would be generated in such slowed areas, skewing the net QRS vector toward them. Thus, an anterolateral infarct, for example, would tend to generate a left-axis deviation on this basis with or without involvement of the conducting system.

Recent evidence: Phase analysis using a variety of approaches[7-10] has found wide clinical and investigative application, primarily as a method for evaluating ventricular regional wall motion abnormalities in the diagnosis of ischemic heart disease. New evidence bearing on putative fascicular block has appeared using phase image characterization of ventricular contraction in patients with a range of left-axis deviation and left-axis deviation combined with right bundle branch block.[11] The investigators used an electrocardiographic-gated blood pool scan using first-harmonic Fourier analysis of the images to determine whether left anterior "hemiblock" was present in patients with left-axis deviation and no contraction abnormalities. They reasoned that phase changes in particular regions would follow their electric activation sequence, and if this was abnormal then myocardial responses would follow the same sequence. In 20 cases of left-axis deviation, including 5 with values of $\geq -60°$, they found no difference in the phase image compared with that in normal control subjects. They conceded that the phase image does not necessarily track the electrical conduction system itself, but definitely expresses the process of regional ventricular contraction accompanying electric conduction. Whereas a possibility of theoretical fascicular block cannot be excluded on the basis of the phase image alone, the results indicate that such isolated disorders of some left anterior "fascicle" without myocardial lesions may well exist, but must be comparatively rare.[11] The authors found no conclusive reason why, in 5 patients with right bundle branch block and left-axis deviation, phase image results more compatible with an anterior fascicular block were noted; however, they offered the hypothesis that left-axis deviation complicated by right bundle branch block is primarily caused by abnormalities exclusively in the conduction system, whereas isolated left-axis deviation could be due to myocardial factors. Meticulous anatomopathologic studies of the left bundle system support this conclusion.[2,3,12]

Evidentiary synopsis (Table I): The report by Ono et al[11] is only the most recent in a large amount of evidence that makes it impossible to conclude from an ordinary electrocardiogram that some kind of fascicular block is present. Fascicular blocks or some equivalent in a very complex system may really exist, but interpretation is confounded by (1) marked anatomic differences in the proximal organization of the left conduction system, (2) any resultant concentration in 2 and ≥3 virtual

TABLE I Fascicular Blocks: Factors Limiting or Rendering Improbable Their Diagnosis from the Electrocardiogram

Basic anatomic complexity and marked intersubject variability of the left bundle system
Most anatomically demonstrable lesions far from sites of electrocardiogram-indicated fascicular interruption
Phase imaging showing ventricular contraction sequence to be unpredictable from sites of electrocardiogram-suggested fascicular blocks
Low probability of lesions strictly confined to the conduction system. Corollary: contribution to net QRS vector (hence axis) of associated or additional myocardial lesions extrinsic to the bundle system
Confounding factor: inherent inaccuracy of the Einthoven equilateral triangle, making axis determination intrinsically imprecise

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(or ultimate) fascicular end-organs, and (3) the common presence of a variety of myocardial abnormalities.[2,4,6,11-13] This is further confounded by the massive inaccuracy of the Einthoven triangle, an equilateral (hence unnatural) assumption that applies with precision only rarely, if ever.[12] (In nature, anything equilateral, smooth, perfectly round or linear must exist only by accident.) We use this triangle because it simplifies construction of a frontal plane axis. Even if the Einthoven triangle could apply to every individual axis confined to the frontal plane of a 3-dimensional structure, axis change must nearly always occur in space rather than only in 1 plane, making the traditional "QRS axis" (shorthand for frontal plane axis) inherently imprecise. Thus, constructing exact axis ranges (e.g., $\leq -45°$) to define an impossible, or at best clinically improbable, diagnosis like fascicular block will introduce other imprecisions.

Conclusion: The electrocardiographer should report exactly what he sees: a frontal plane axis based on the Einthoven triangle. The consumer of this information will understand that one of the possibilities of marked axis deviation from normal is a fascicular block, actual or virtual (i.e., an equivalent at the anterosuperior or posterior extreme of the complex left conducting system), but it is misleading to use those terms in electrocardiographic interpretation when an electrocardiographic axis cannot provide precise and certainly not conclusive evidence. On the other hand, to use the kind of physiologic thinking introduced by Rosenbaum et al[1] is an important adjunct to electrocardiography and should not be neglected. Meanwhile, it is to be hoped that the electrophysiologists will further develop clinical electrophysiology of the bundle branches to bring us nearer to an acceptable resolution of this problem.

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Low High-Density Lipoprotein Cholesterol and What to Do About It*

William B. Kannel, MD

Blood lipids are fundamental in atherogenesis. Control of lipids is acknowledged as essential in prevention of coronary disease by the federal guidelines that focus on total cholesterol and its low-density lipoprotein (LDL) cholesterol component.[1] Despite the demonstrated strong relation of low high-density lipoprotein (HDL) cholesterol to the occurrence of coronary artery disease (CAD) and the biologic plausibility of the relation, the Federal guidelines have been circumspect concerning HDL cholesterol. The understanding of the HDL metabolism was considered by the expert panel to be too primitive and laboratory measurement of HDL cholesterol too inaccurate on which to base clinical decisions.[1] Also, there has not yet been a clinical trial conducted to test whether raising HDL alone reduces risk of CAD independent of lowering LDL cholesterol. The recently revised guidelines recommend HDL cholesterol determination on all persons having cholesterol measured, but they fail to take into consideration the benefits of a high HDL cholesterol resulting in an acceptable total/HDL cholesterol ratio despite an elevated total cholesterol or LDL cholesterol. Recommendations concerning triglycerides also fail to take adequately into account the heterogeneity of this entity, its importance in choosing lipid-lowering agents and its importance as an indicator of the metabolic problem.

Epidemiologic data consistently demonstrate that there is a protective HDL cholesterol component involved in removal of cholesterol from the tissues which

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This study was supported by the Charles A. Dana Foundation, New York, New York, Merck, Sharpe & Dohme, Rahway, New Jersey, and Grants N01-HV-92922 and N01-HV-52971 from the National Institutes of Health, Bethesda, Maryland. Manuscript received March 9, 1992; revised manuscript received and accepted May 11, 1992.

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*Presented at the National Heart, Lung, and Blood Institute Conference on Cholesterol and High Blood Pressure, Washington, D.C., April 1991.

TABLE I Average Lipid Values in Patients with Coronary Artery Disease*

	Average Values (mg/dl)			
	Age 50–64 Years		Age 65–84 Years	
Cholesterol	Men	Women	Men	Women
Total	227	249	223	247
HDL	43	53	44	52
LDL	151	166	146	162
TC/HDL	5.6	5.0	5.5	5.1

*Subjects aged 50 to 84 years (The Framingham Study).
HDL = high-density lipoprotein; LDL = low-density lipoprotein; TC = total cholesterol.

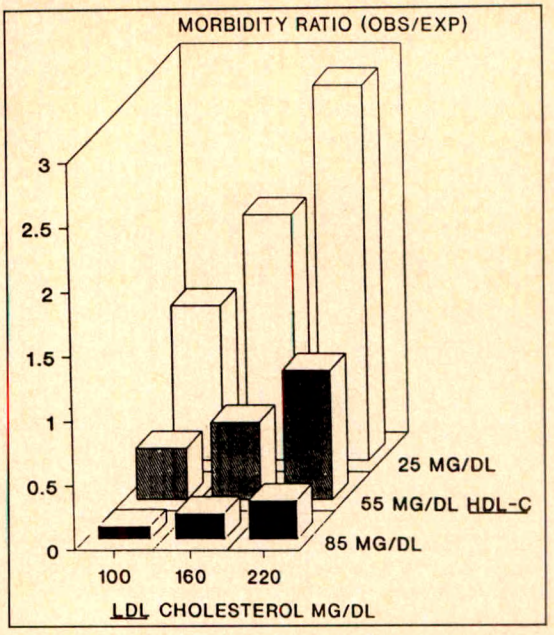


FIGURE 1. Coronary artery disease by high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C) in 50- to 70-year-old men (Framingham Study). EXP = expected; OBS = observed. (Adapted from *American Heart Journal* 1985;110:1100.)

powerfully influences the CAD risk at any LDL cholesterol level (Figure 1). This is only partially taken into account by the national guidelines which recognize a low HDL cholesterol as an additional risk factor to be invoked when the LDL cholesterol is in the borderline (130 to 159 mg/dl) range.[1] The protective effect of an elevated HDL cholesterol must be considered if we are to avoid needlessly alarming or treating potential coronary candidates (Figure 1). It is imperative when considering action based on the serum total or LDL cholesterol to know the accompanying HDL cholesterol in order to evaluate properly lipid-induced CAD risk.

Examination of the average lipid values at which CAD events have occurred in the Framingham Study over the past 3 decades in men indicates that half the events are occurring at values the guidelines designate as borderline or safe. In women, the average total and LDL cholesterols of those sustaining CAD events have been only slightly above the values recommended for treatment (Table I). This indicates the need for a more sensitive and specific lipid profile. The guidelines as currently specified require that we treat 30 to 40% of the adult population.

The total/HDL cholesterol ratio constitutes a more convenient and efficient profile because it reflects the joint effect of the 2-way traffic of cholesterol entering and leaving the tissues. This does not require a fasting specimen or a triglyceride determination in order to estimate LDL cholesterol. This ratio predicts CAD as accurately as the theoretically superior LDL/HDL cholesterol ratio and as efficiently as a linear combination of these lipid components.[2]

Risk of developing CAD increases steeply with small increments in this ratio in either sex (Figure 2). A ratio of 3.5, which corresponds to one half the high average North American risk of CAD, appears optimal and women lose their CAD vulnerability advantage over men at ratios of >7.5. HDL cholesterol remains a significant independent predictor of CAD, even taking highly (inversely) correlated triglyceride and all the other CAD risk factors into account.[2,3] Furthermore, low HDL cholesterol is also associated with excess overall

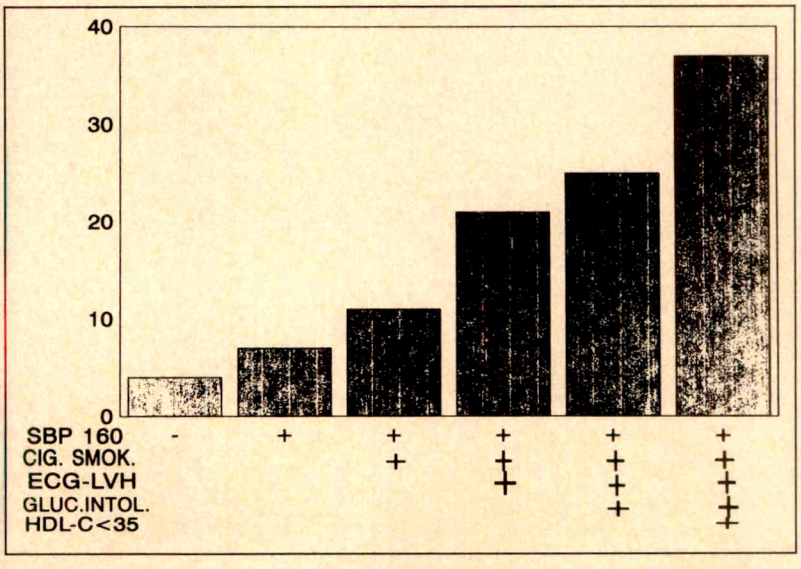


FIGURE 2. Risk of coronary artery disease at serum cholesterol of 240 mg/dl according to other cardiovascular risk factors in men aged 50 years (Framingham Study). CIG. SMOK. = cigarette smoking; ECG = electrocardiogram; GLUC.INTOL. = glucose intolerance; HDL-C = high-density lipoprotein cholesterol; LVH = left ventricular hypertrophy; SBP = systolic blood pressure.

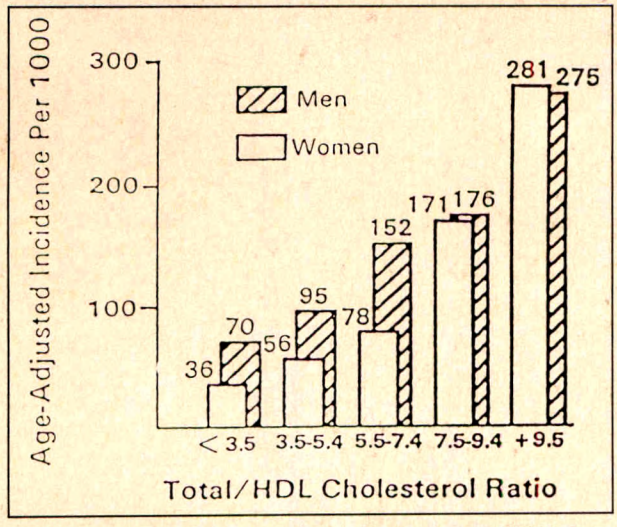


FIGURE 3. Risk of coronary artery disease by total/high-density lipoprotein (HDL) cholesterol among men and women aged 50 to 90 years (Framingham Study — 26-year follow-up).

mortality and increased HDL cholesterol is unrelated to cancer mortality. The strength of the relation of HDL cholesterol with CAD risk is more consistently maintained through all age groups, including the elderly, than it is for LDL total cholesterol.

Regression analysis of the Framingham study data standardizing for the different range of values indicates that the impact of HDL cholesterol is twice that of LDL cholesterol.[2] This Framingham study finding is confirmed in the Helsinki Trial which also found a two-fold greater impact of HDL cholesterol than LDL cholesterol.[4]

In support of epidemiologic data on the importance of HDL cholesterol in CAD, there is a great deal of data indicating a strong correlation between HDL and anatomic coronary artery occlusive disease found at cardiac catheterization, even in persons with acceptable total and LDL cholesterol levels, but with a poor total/HDL cholesterol ratio.[5]

For the most accurate assessment of the urgency of treatment for lipid aberrations it is necessary to also

TABLE II Coronary Artery Disease Risk Factor Prediction Chart

Age (if female)		Age (if male)		HDL Cholesterol		Total Cholesterol		Systolic Blood Pressure			
Age (yr)	Pts.	Age (yr)	Pts.	Age (yr)	Pts.	Age (yr)	Pts.	HDL-C	Pts.	Total-C	Pts.	SBP	Pts.	Other	Pts.
Find Points for Each Risk Factor															
30	−12	47–48	5	30	−2	57–59	13	25–26	7	139–151	−3	98–104	−2	Cigarettes	4
31	−11	49–50	6	31	−1	60–61	14	27–29	6	152–166	−2	105–112	−1	Diabetic-men	3
32	−9	51–52	7	32–33	0	62–64	15	30–32	5	167–182	−1	113–120	0	Diabetic-women	6
33	−8	53–55	8	34	1	65–67	16	33–35	4	183–199	0	121–129	1	ECG-LVH	9
34	−6	56–60	9	35–36	2	68–70	17	36–38	3	200–219	1	130–139	2		
35	−5	61–67	10	37–38	3	71–73	18	39–42	2	220–239	2	140–149	3	0 pts. for each	No
36	−4	68–74	11	39	4	74	19	43–46	1	240–262	3	150–160	4		
37	−3			40–41	5			47–50	0	263–288	4	161–172	5		
38	−2			42–43	6			51–55	−1	289–315	5	173–185	6		
39	−1			44–45	7			56–60	−2	316–330	6				
40	0			46–47	8			61–66	−3						
41	1			48–49	9			67–73	−4						
42–43	2			50–51	10			74–80	−5						
44	3			52–54	11			81–87	−6						
45–46	4			55–56	12			88–96	−7						

____ Age + ____ HDL-C + ____ Total-C + ____ SBP + ____ Smoker + ____ Diabetes + ____ ECG-LVH = ____ Point Total

NOTE: Minus Points Subtract from Total

Look Up Risk Corresponding to Point Total												Compare with Average 10-Year Risk		
Probability			Probability			Probability			Probability			Probability		
Pts.	5 Yr.	10 Yr.	Pts.	5 Yr.	10 Yr.	Pts.	5 Yr.	10 Yr.	Pts.	5 Yr.	10 Yr.	Age (yr)	Women	Men
Sum Points for All Risk Factors														
≤1	<1%	<2%	10	2%	6%	19	8%	16%	28	19%	33%	30–34	<1%	3%
2	1%	2%	11	3%	6%	20	8%	18%	29	20%	36%	35–39	<1%	5%
3	1%	2%	12	3%	7%	21	9%	19%	30	22%	38%	40–44	2%	6%
4	1%	2%	13	3%	8%	22	11%	21%	31	24%	40%	45–49	5%	10%
5	1%	3%	14	4%	9%	23	12%	23%	32	25%	42%	50–54	8%	14%
6	1%	3%	15	5%	10%	24	13%	25%				55–59	12%	16%
7	1%	4%	16	5%	12%	25	14%	27%				60–64	13%	21%
8	2%	4%	17	6%	13%	26	16%	29%				65–69	9%	30%
9	2%	5%	18	7%	14%	27	17%	31%				70–74	12%	24%

Adapted from the Framingham Heart Study, the American Heart Association.
C = cholesterol; ECG = electrocardiogram; HDL = high-density lipoprotein; LVH = left ventricular hypertrophy; SBP = systolic blood pressure.

take into account other coexistent cardiovascular risk factors because they markedly influence the lipid-induced CAD risk.[6] The risk associated with an elevated serum total cholesterol (or LDL cholesterol) varies over a 10-fold range depending on the number of these associated risk factors (Figure 3).

A risk factor must have a biologically plausible relation to disease to be etiologic. A number of possible mechanisms have been postulated whereby HDL protects against development of CAD. It has been found to be a scavenger for surface-active products of lipolysis and to have a role in reverse cholesterol transport.[7] It has also been shown to stimulate prostacyclin synthesis. It is unlikely that it is only a reflection of a more fundamental disorder of another class of lipoproteins.

Preventive options: Fortunately, most of the hygienic measures advocated for avoiding CAD also tend to raise HDL cholesterol including: weight reduction, exercise and quitting smoking.[7,8] Weight control is especially important since it also improves most of the major risk factors such as elevated blood pressure, uric acid and glucose intolerance.[9] More than 6 miles of endurance exercise per week will raise HDL cholesterol significantly, especially the HDL-2 subfraction. Moderate alcohol intake can also raise HDL cholesterol.[7]

A number of drugs can also be used to raise HDL cholesterol. Estrogen use in women can raise HDL cholesterol and lower LDL cholesterol but will also raise triglycerides.[7,8] Hypertension, whether or not treated, is associated with a greater prevalence of increased serum total cholesterol, LDL cholesterol and triglyceride and a reduced HDL cholesterol. Unfortunately, some antihypertensive agents such as β blockers and diuretics adversely affect lipids and are best avoided if the objective is to prevent coronary disease.[7,8]

A number of pharmaceuticals are available which are capable of improving the lipid profile through different modes of action without producing intolerable side effects.[7] Used singly or in combination these drugs can effect substantial improvements in most lipid disorders encountered in clinical practice. Gemfibrozil and nicotinic acid raise HDL cholesterol and reduce triglycerides particularly well. Hydroxymethylglutarate-glutaraldehyde reductase inhibitors such as lovastatin, simvastatin and pravastatin will effectively lower LDL cholesterol and moderately increase HDL cholesterol. Even bile-sequestering resins which lower LDL cholesterol raise HDL cholesterol somewhat. Thus, most agents frequently used to correct lipid aberrations raise HDL cholesterol and improve the total/HDL cholesterol ratio. Only probucol reduces HDL cholesterol and can only be recommended for its antioxidant properties.

Evidence of efficacy: The Helsinki Trial found the incidence of reduction in CAD most strongly related to the degree to which HDL cholesterol was raised by gemfibrozil. Gemfibrozil was found to be most effective in those who had a low HDL cholesterol and elevated triglycerides.[4] This trial also found that persons with a high total/HDL cholesterol combined with triglycerides of >200 mg/dl had a disproportionately higher risk of coronary disease than those with a high ratio unaccompanied by elevated triglycerides.[10] This further supports a recommendation to treat low HDL cholesterol because this subgroup with the combination of high triglyceride and low HDL had the greatest reduction in incidence of coronary disease among those receiving treatment. The Coronary Drug Project found nicotinic acid to be effective in secondary prevention.[11] This drug also raises HDL cholesterol and reduces triglyceride. In the Lipid Research Clinics trial, a 2.8% increase in HDL cholesterol was achieved with cholestyramine therapy, and this was found to have an independent effect in reducing CAD events.[7] The National Heart, Lung, and Blood Institute Type II Coronary Intervention Study, examining the angiographic effects of cholestyramine in persons with established coronary disease, found that the 6% increment in HDL cholesterol achieved was inversely related to progression of CAD independent of the reduction in LDL cholesterol achieved.[7,12] In the study of Brown et al,[13] colestipol plus niacin produced the greatest regression of lesions on angiography.

Risk assessment: Recently published data from the Physicians' Health Study confirms the Framingham study data indicating that the total/HDL ratio is the most efficient lipid profile for predicting CAD and demonstrates that both HDL-2 and HDL-3 subfractions are strongly inversely related to occurrence of myocardial infarctions.[14]

A selection of candidates for treatment is best done using a multivariate CAD risk scoring system that targets those truly in jeopardy, avoiding needlessly treating or falsely reassuring coronary candidates. Such a risk profile is available from the American Heart Association, derived from multivariate analysis of Framingham study data.[6] This enables a quantitative assessment of the conditional probability of a CAD event for any combination of risk factors (Table II), incorporating the lipids as ingredients of a comprehensive risk profile. The relevant risk factors can be readily measured using ordinary office procedures and simple laboratory tests in a nonfasting patient. It has been estimated that, using the national guidelines without such a risk profile, it is necessary to treat 350 patients each year to benefit one.

Guidelines for treatment: For those at high risk because of a poor cardiovascular profile and unresponsive to hygienic measures, treatment with pharmaceuticals would appear justified if the LDL cholesterol is >160 mg/dl. Hygienic, nonpharmacologic measures can be recommended for those with a total/HDL cholesterol ratio >5.0, but with LDL cholesterol <160 mg/dl. Proof of the efficacy of raising HDL cholesterol in the absence of a concomitant lowering of LDL cholesterol is lacking (and incidentally, so is the converse). However, the Helsinki and Coronary Drug Project trials strongly suggest efficacy of raising HDL cholesterol.

There is reason to be concerned about an elevated triglyceride that accompanies a poor total/HDL cholesterol ratio because this subgroup was found to have an inordinately high risk of CAD in the Helsinki Study, and responded best to gemfibrozil therapy.[9] High triglycerides beget reduced HDL cholesterol so that persons with high triglycerides can be expected to develop an excess of CAD. A greater reduction in total/HDL

cholesterol ratio can be achieved in such persons using gemfibrozil or nicotinic acid. For those with an isolated LDL cholesterol elevation, a hydroxymethylglutaryl coenzyme A Reductase inhibitor or a resin offer the greatest potential for improving the total/HDL cholesterol ratio.[15]

Small, dense triglyceride particles may be directly atherogenic, leading to cholesterol ester deposition. Also, elevated triglyceride levels are clearly components to Reaven's Syndrome X which, along with insulin-resistance and low HDL, denotes accelerated atherogenesis.

The size of the population at risk of CAD with unacceptable HDL cholesterol levels cannot be ignored and warrants a major clinical trial. Some 10% of the population have HDL cholesterol <35 mg/dl and 5% <30 mg/dl.[7] This indicates that some 10 to 20 million persons in the USA are in jeopardy. Hence, a definitive clinical trial would appear to be long overdue.

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Cardiac Transplant Recipients Are Sex Blind to Their Heart Donors

Mary Moore Free, PhD

The Feminist Reading Group, founded by the Director of the Women's Studies Program at Southern Methodist University (SMU), presents 3 symposia each year. The meetings are held on campus in the informal surroundings of the Faculty Club. This group is composed of members of both the SMU faculty and the Women's Studies Network, the nonuniversity arm. Its central focus is to delineate how biologic sex has a problematic effect on different disciplines. Because women's studies programs are traditionally interdisciplinary, the Feminist Reading Group serves as a forum for getting its members to explore how disciplines other than their own treat issues of sex. The central focus of this meeting was to delineate how biologic sex has a problematic effect on different disciplines. (I designate the term "sex" to denote biologic differences between men and women, whereas the term "gender" is a symbolic category of cultural and psychosocial beliefs that determine masculinity and femininity in a given society.) The third and final meeting of this year centered on "Women in Science."

While the symposia are not limited to women, all 18 participants present on this occasion were women; these included 13 PhDs from the fields of anthropology (ethnologic, medical and physical), art history, dance, English, French language and literature, history, political science and sociology, 2 JDs from the SMU School of Law, 2 MDs from the Women's Network, and 1 Women's Network representative who is a specialist in domestic violence. In preparation for the discussion at the meeting, 4 papers dealing with both the rank and status of women in science and the assumption that scientific research is value-free had been mailed earlier to each participant.

A plethora of data from both published and anecdotal reports confirm unequivocally that women in medical, natural and social sciences (as well as in all other areas of the public domain) are subjected to sex bias. Although this well-known issue was once again discussed in a thorough and lively fashion that yielded a

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variety of both old and new opinions and theories for dealing with it, this topic is not the subject of my comment. Instead, my purpose is to call attention to an event that has no sex bias; namely, cardiac transplantation (CT).

The director of the program introduced 1 of the MDs (a neuropsychologist) who served as facilitator. She is presently affiliated with the University of Texas Southwestern Medical Center at Dallas (UTSMCD) and received training (1980 to 1984) at the National Institutes of Health (NIH). She recently decided to leave the medical milieu and has accepted an appointment at Duke University in the Department of Psychology to begin in the 1992 fall semester. Her opening remarks concerning her experiences with sex bias in medicine at UTSMCD and NIH stimulated much intellectual exploration of the issue in general. Everybody present took part in the discussion.

I am House Anthropologist at Baylor University Medical Center (BUMC). (Anthropology is the cross-cultural and comparative study of human behavior.) One of my appointments is to the CT interdisciplinary team for the purpose of assessing subjectively perceived well-being among heart transplant recipients (and candidates). My comments, stimulated by this meeting of the Feminist Reading Group, are based on my experience of 17 months in that medical service. While CT recipients are also blind to the age, color and ethnicity of the donors of their new hearts, over time come to think and speak of their cardiac transplants not as "new" hearts, but as their "own" hearts, and refer to themselves by their transplant "number" (e.g., "I am number 26"), this discussion will be limited to the matter of the absence of sex bias.

When a cardiac patient is faced with his or her mortality and CT is the only therapy deemed to reduce one's chance of death, all other issues not only pale, but disappear altogether. It does not matter to a female CT recipient whether her donor heart is that of a man or woman; conversely, it does not matter to a male CT recipient whether his donor heart is that of a woman or man. This is made apparent as recipients discuss this issue in formal settings (e.g., support group and clinic) and informal settings (e.g., the New Hearts meetings [BUMC's CT club], BUMC Transplant Reunion, CT family picnic and New Year's Day CT party at the home of "Dr. A." [Dr. Peter A. Alivizatos, Chief of Cardiothoracic Transplantation Service, BUMC]). It is indeed a fact that CT recipients are sex blind to their heart donors.

The following description of the experience of a middle-aged male CT recipient is taken from data recorded in my field notes:

"I was given 6 to 9 months to live. After my bypass operation, my heart was working at only 18% capacity, and the doctors told me that more bypass surgery would not help me. When they told me I needed a new heart, my only thought was, 'well, I have got to have a new heart. What do I do now?' You get pretty close to death and lie in bed and think about what this means or may mean. You get second feelings — those are doubts about the outcome. It is so stressful waiting for a heart to become available. I did not care whose heart it was — man, woman, black, yellow, red or white. I was so weak I could not complain even if I wanted to, and nothing — TV, songs, absolutely *nothing* — seemed important. Then, when the call came that they had a heart, I was not joyful. I wanted to back out; I was not frightened, but the timing was so bad because a lot was going on at home. Finally I decided to go. I had 2 hours. I said to my son, 'I have got to go or I will not make it.' My mother asked me how I felt, and I said fine. She wanted to know if I really wanted to go through with it. I told her I had asked for her support a long time ago and she had given it to me. She then said, 'okay, go.' I went. My wife drove me. I feel like I have been given a third life; that is, I was given life when I was born with my first heart; then, I had my bypass which was my second life; now, I have my new heart and a third life. When I woke up and felt my heart beating and they told me I had a new heart, I was glad and I said, 'thank God.' I have not lost anything in life, and my quality of life has jumped. It is a great experience, a new heart. I just hope I can continue to handle it as well as all the other 'New Hearts.' I put my faith in 'Dr. A.' and the other doctors — all of them are the best—and they elevated me back into my own personality. Believe the doctors if they say you need a transplant. I had not felt sick when it was discovered. I was put in the hospital as a candidate 2 months later. I could walk only a few steps and had to be wheeled into the hospital. When I asked the doctors what I could do afterwards, they said that soon I could do everything. I went through cardiac rehabilitation. While I know I am not a teenager, I plan to get out there and act like one. And now I think I feel better than ever before in my life. My new heart seems stronger than my old heart was even before I was sick. I am more perceptive, more sensitive and more understanding. *And, yes, the donor of my new heart was a woman!*"

Incidence and Prognostic Significance of Chronic Atrial Fibrillation Among 5,839 Consecutive Patients with Acute Myocardial Infarction

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Paroxysmal atrial fibrillation (AF), a frequent complication of acute myocardial infarction (AMI), was found to be a weak independent predictor of the long-term mortality in surviving patients in 2 recent studies.[1,2] We are unaware of any studies on the prognostic impact of chronic AF on patients with AMI. The present study assesses the short- and long-term outcomes of patients with chronic AF having an AMI.

The data reported here were obtained from the Secondary Prevention Reinfarction Israeli Nifedipine Trial (SPRINT) registry that includes 5,839 consecutive patients with AMI hospitalized in 13 of 21 coronary care units in Israel from 1981 to 1983. The diagnosis of AMI was based on presence of new Q/QS changes on the electrocardiogram, significant increase in cardiac enzymes (creatine kinase, glutamine oxalotransaminase and lactate dehydrogenase), and presence of typical symptoms lasting ≥30 minutes. Chronic AF was diagnosed by history, comparison with previous electrocardiograms (when available), and persistent presence of the arrhythmia during hospitalization and on discharge from hospital. Forty-one patients (0.7%) fulfilled the diagnostic criteria of chronic AF.

The prevalence of chronic AF was significantly higher in women. The characteristics of patients with and without chronic AF are compared in Table I. Patients with chronic AF were older and had angina, AMI, cerebrovascular accidents and peripheral vascular disease in the past more often than did those without AF. Before the index AMI, chronic AF was associated with ischemic heart disease in 20 patients, hypertension in 12 and rheumatic heart disease in 1.

The hospital course of patients with and without chronic AF is shown in Table II. On admission to coronary care units, a high Killip class grade, and cardiomegaly and pulmonary congestion or edema on the chest x-ray were more frequent in patients with chronic AF. However, during hospitalization major complications were equally present in both groups. Systemic peripheral emboli and cerebrovascular accidents or transient ischemic attacks occurred in 3 of 41 patients (7%) with chronic AF compared with 57 of 5,798 (1%) in sinus rhythm (Table II).

On hospital discharge, anticoagulant or antiplatelet aggregant treatment was administered to only 7 of 35 surviving patients (20%) with chronic AF, a proportion comparable to the 910 of 4,773 (19%) in the reference group. The low rate of antithrombotic treatment in the group of AF patients was probably related to the absence of guidelines for treatment of nonrheumatic AF at the time. During the first year of follow-up, the rate of

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TABLE I Characteristics of Patients with Chronic Atrial Fibrillation During Acute Myocardial Infarction

	Chronic AF		
	Present (n = 41)	Absent (n = 5,798)	p Value
Men	23 (56%)	4,292 (74%)	<0.05
Age (yr)	71 ± 7	63 ± 11	<0.005
History			
Acute myocardial infarction	16 (39%)	1,415 (24%)	<0.05
Angina pectoris	27 (66%)	2,840 (49%)	0.06
Hypertension	12 (29%)	2,299 (40%)	NS
Diabetes mellitus	13 (22%)	1,189 (21%)	NS
Peripheral vascular disease	7 (18%)	446 (8%)	<0.01
Systemic peripheral emboli	3 (7%)	57 (1%)	<0.0001

AF = atrial fibrillation; NS = not significant.

TABLE II Hospital Course of Patients with Chronic Atrial Fibrillation During Acute Myocardial Infarction

	Chronic AF				
	Present (n = 41)		Absent (n = 5,798)		
	No.	%	No.	%	p Value
Admission					
Killip class					<0.0001
I	18	44	4,311	74	
II–IV	23	56	1,441	25	
Unknown	—	—	23	<1	
Chest x-ray					
Cardiomegaly	25	61	1,614	28	<0.0001
Pulmonary congestion or edema	18	44	1,440	25	<0.002
AMI type and location					<0.05
Non-Q-wave	7	17	444	8	
Q-wave					
Anterior	16	39	2,549	44	
Inferior	11	27	2,253	39	
High enzyme level (>4/nl)					NS
Creatine kinase	18	44	3,077	53	
Glutamic oxalotransaminase	11	27	2,367	41	
Lactic dehydrogenase	2	5	710	12	
In-hospital complications					
Cardiac arrest	3	7	441	8	NS
Ventricular tachycardia	9	22	1,021	18	NS
Ventricular fibrillation	2	5	407	7	NS
Advanced atrioventricular block	1	2	648	11	0.05
Congestive heart failure	11	27	1,264	22	0.07
Cardiogenic shock	2	5	491	8	NS
Stroke, systemic emboli	3	7	57	1	0.008
Mortality					
Hospital	6	15	1,025	18	NS
Postdischarge					
1 year	7	20	443	9	<0.05
5 years	20	57	1,302	27	<0.0005

Abbreviations as in Table I.

cerebrovascular accidents or transient ischemic attacks in patients with chronic AF (3 of 35; 9%) was significantly increased in comparison with that in the reference group (45 of 4,773; 1%) ($p < 0.0001$). None of the 3 patients with chronic AF who had a stroke and 8 of the 45 in the reference group were receiving antiplatelet drugs when the cerebrovascular accident occurred.

The in-hospital mortality rate was similar in patients with and without chronic AF (Table II). However, a significant excess of mortality was observed at 1 and 5 years after discharge in patients with chronic AF (Table II). Figure 1 shows the actuarial 5-year survival in the 2 groups. The association between chronic AF and long-term mortality, using a Cox proportional hazard model adjusting for age as well as additional clinical indicators for subsequent mortality (gender, history of AMI, angina pectoris, cerebrovascular accidents and major complications during hospitalization), was calculated in the overall sample of 4,808 surviving patients with AMI. The relative risk of mortality 5 years after discharge in patients with chronic AF was 1.25 (90% confidence interval 0.85 to 1.79), indicating that chronic AF is more likely a marker rather than an independent predictor of late mortality.

The prevalence and outcome of patients with chronic AF experiencing AMI have been seldom reported.[3] In this study, the 0.7% prevalence of chronic AF among 5,839 patients with AMI is in accordance with previous studies. In the Coronary Artery Surgery Study (CASS), the prevalence of chronic AF was 0.6% (118 of 18,343 subjects).[4] In the Framingham Study, chronic AF was a relatively uncommon arrhythmia (98 of 5,191 subjects over a 22-year period) with little relation to coronary artery disease in the absence of heart failure.[5]

Chronic AF increased the risk of stroke after discharge ninefold. In several recent studies, nonrheumatic chronic AF was associated with a five- to sixfold increased risk for stroke in comparison with matched populations with sinus rhythm.[6,7]

The recent positive clinical trials on stroke prevention in chronic AF[6–8] with anticoagulants or aspirin and the relatively high risk of stroke among AMI patients with chronic AF reinforce the necessity to provide antiplatelet or anticoagulant treatment to these patients.

APPENDIX

SPRINT study group: EXECUTIVE BOARD: Henry N. Neufeld, MD, Chairman (deceased); Jacob Agmon, MD, Vice Chairman; Solomon Behar, MD; Uri Goldbourt, PhD; Henrietta Reicher-Reiss, MD; Edward Abinader, MD; Jacob Barzilay, MD; Natalio Cristal, MD; Yaacov Friedman, MD; Nissim Kauli, MD; Yehezkiel Kishon, MD; Abraham Palant, MD; Benyamin Peled, MD; Leonardo Reisin, MD; Egon Riss, MD (deceased); Zwi Schlesinger, MD; Izhar Zahavi, MD; and Monty Zion, MD.

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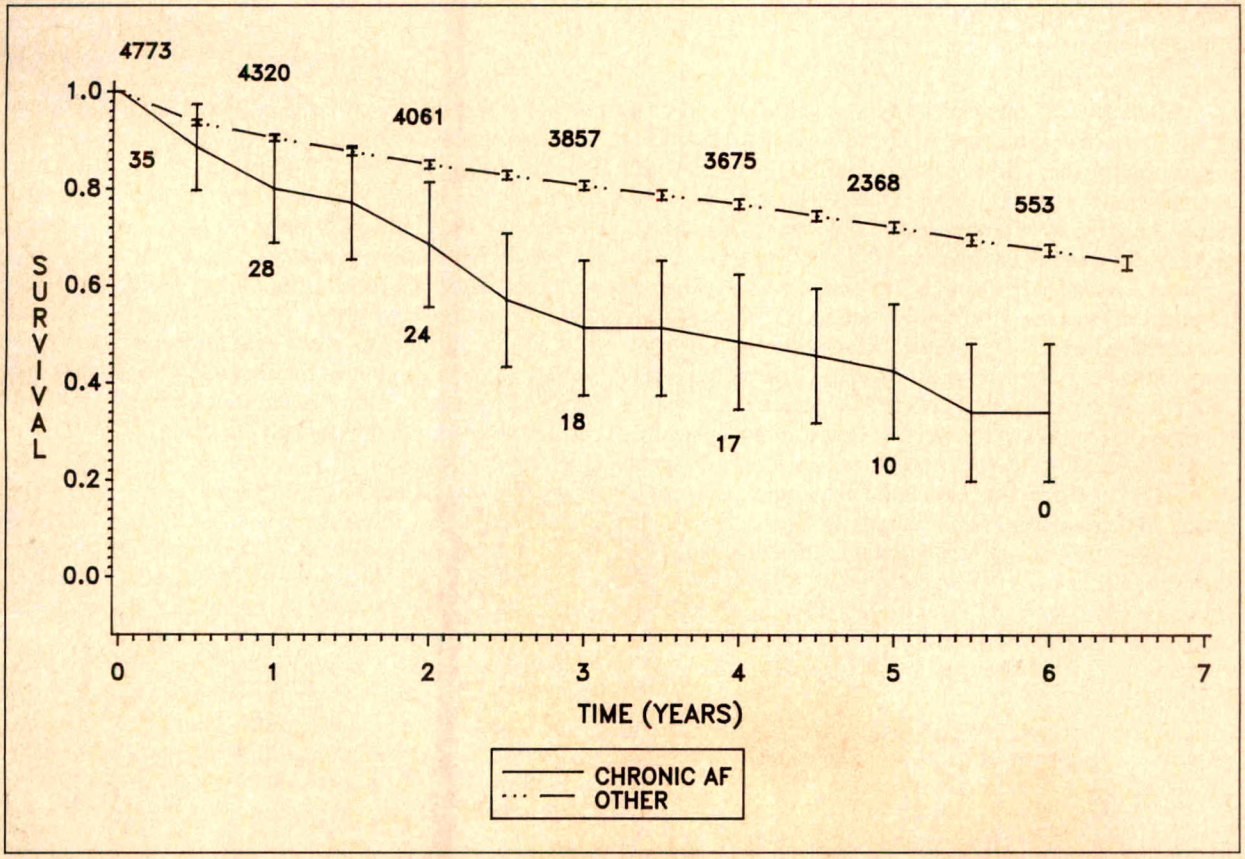


FIGURE 1. Actuarial survival curve of patients with and without chronic atrial fibrillation (AF) after acute myocardia infarction.

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Prevalence of Pseudoischemic ST-Segment Changes During Ambulatory Electrocardiographic Monitoring

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Ambulatory electrocardiographic monitoring (AEM) is frequently used to record ST-segment changes suggesting transient myocardial ischemia in patients with coronary artery disease.[1] AEM has also been used to assess the efficacy of antiischemic therapy.[2–6] The value of AEM for ischemia monitoring is dependent on the ST-segment changes detected being reliable markers for transient myocardial ischemia. Frequently, before AEM and exercise treadmill tests, technicians perform provocative maneuvers (i.e., position change, hyperventilation and Valsalva maneuver) to elicit ST-segment or T-wave changes that may interfere with electrocardiographic determinations of transient myocardial ischemia. Despite this practice, there are few studies examining the incidence of these electrocardiographic artifacts. One such study found that in subjects without cardiac disease, ST-segment depression or T-wave changes suggesting ischemia seldom occurred.[7] The aim of this study was to determine the prevalence of these pseudoischemic ST-segment or T-wave changes in cardiac patients referred for AEM.

The study group comprised 100 patients (66 men and 34 women, age range 18 to 80 years, mean 52.8) referred for AEM evaluation of arrhythmias or transient myocardial ischemia. Forty-three patients had documented atherosclerotic heart disease by coronary angiography. Patients with baseline ST-segment abnormalities or bundle branch blocks that would hinder any ST-segment interpretation of ischemia were excluded. All patients gave informed consent to participate in the study.

Ambulatory electrocardiographic recordings were obtained using commercially available AM, FM and real-time ambulatory electrocardiographic monitors calibrated for ST-segment monitoring. Two leads (modified lead 2 and V_5) were monitored and analyzed, and the ST segments were verified visually to be as close to isoelectric as possible. Five-second electrocardiographic strips from both leads were recorded in each subject after 2 minutes in the following positions: sitting, standing erect, laying prone, supine and in the right and left lateral positions. Recordings were also obtained after 30 seconds of hyperventilation and during the Valsalva maneuver.

Changes in the ST segment and T wave were assessed. The electrocardiographic strip recorded in the sitting position was considered baseline. The ST segment was analyzed for persistent shifts ≥0.5 mm from baseline occurring 80 ms after the QRS complex. The T wave was inspected for persistent axis shifts ≥90° from baseline.

Electrocardiographic recordings from both leads were also evaluated after 1 cm shifts of the electrode

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Manuscript received February 3, 1992; revised manuscript revised April 27, 1992, and accepted May 1, 1992.

TABLE I Number of Patients with ST-Segment and T-Wave Changes Induced by Physiologic Maneuvers

	Position		Hyperventilation		Valsalva		Total	
	M	F	M	F	M	F	M	F
ST ↓ 0.5 mm	20	5	3	3	2	2	20	6
ST ↓ 1 mm	4*	2	3†	0	2†	0	5	2
90° T-axis change	13	10	5	5	3	4	15	12
180° T-axis change	4	4	0	2	0	4	4	7

*Two patients with isoelectric baseline.
†One patient with isoelectric baseline.
↓ = depression.

position from baseline in 4 directions (cephalad, caudal, left and right) in 25 patients. The initial measurements were considered baseline. After each of the four 1 cm electrode shifts, electrocardiographic strips were recorded after various position changes and compared with baseline in the aforementioned manner.

In all, 32 patients (25 men and 7 women) developed ≥0.5 mm ST-segment depression with either a change in body position or during hyperventilation or the Valsalva maneuver. Of these patients, ≥1 mm flat ST-segment depression was noted in 7 (5 men and 2 women), 4 of whom had an isoelectric baseline (Figures 1 and 2). T-wave changes occurred in 38 patients. Eleven patients demonstrated 180° T-wave axis shifts (Figure 2). These results are listed in Table I.

ST-segment elevation ≥1 mm over baseline occurred in 6 patients (4 men and 2 women). Four men had ST-segment elevation ≥1 mm over baseline with position changes (2 from an isoelectric baseline). Hyperventilation and the Valsalva maneuver induced the ST-segment elevation from an isoelectric baseline in 2 women.

ST-segment changes after 1 cm electrode shifts were examined in 1,200 electrocardiographic strips. An isoelectric baseline was identified in 744 strips (62%). Electrode shifts induced ST-segment depression ≥0.5 mm in 24 of 744 electrocardiographic strips (3%) from an isoelectric baseline and in 102 of 456 (22%) with an abnor-

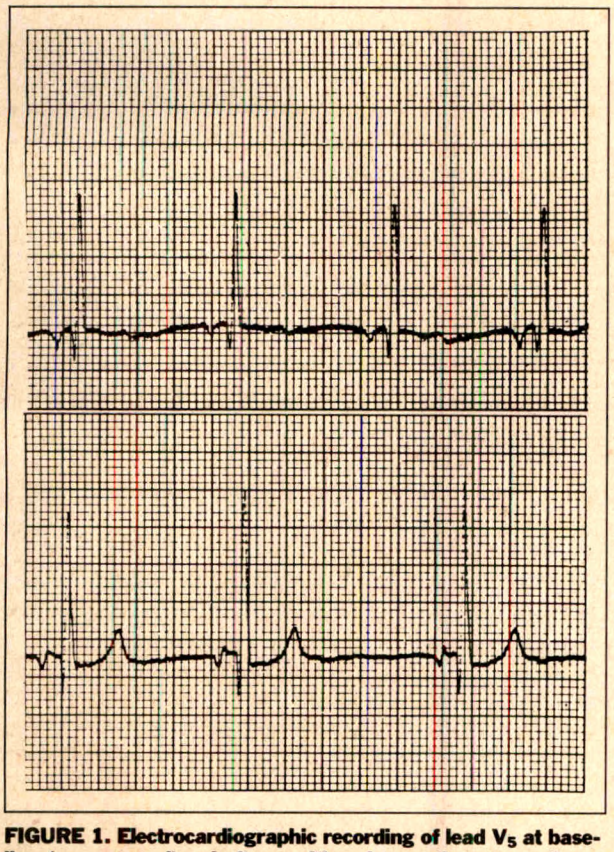


FIGURE 1. Electrocardiographic recording of lead V_5 at baseline *(upper panel)* and after position change *(lower panel)*. Note 1 mm ST-segment depression and 90° T-wave axis shift after standing erect.

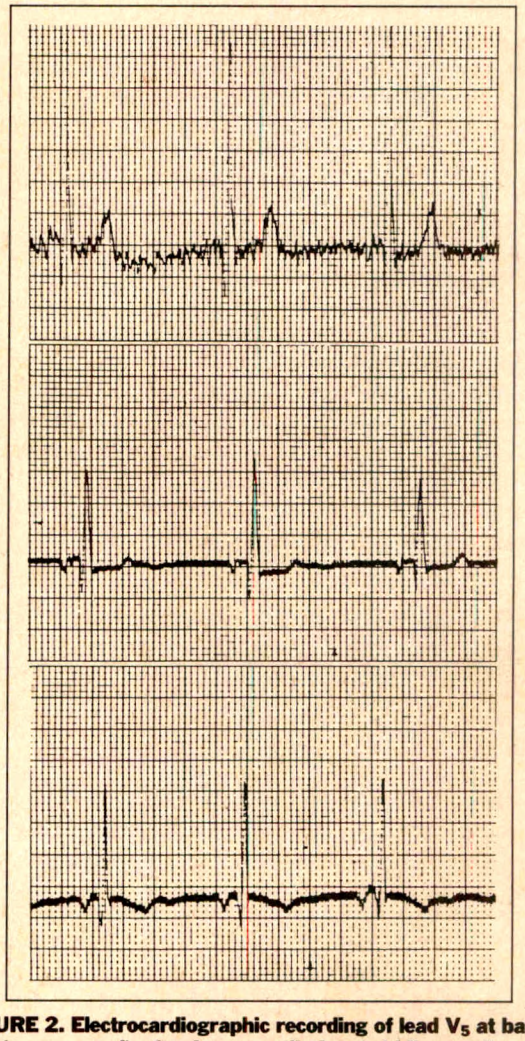


FIGURE 2. Electrocardiographic recording of lead V_5 at baseline *(upper panel)*, after hyperventilation *(middle panel)* and with Valsalva maneuver *(lower panel)*. Note 1 mm ST-segment depression after hyperventilation, and 180° T-wave axis shift after Valsalva maneuver.

TABLE II Percentage of Cardiac Patients with ST-T Changes Induced by Physiologic Maneuvers

Study	Total Pts.	1 mm ST ↓	T-Wave 90° Change	T-Wave 180° Change	Provocation
Past studies					
Bellet & Roman[8]	1,096	0.3	—	5	Position
Golden et al[9]	72	—	1	1	Hyperventilation
Wasserburger et al[10]	350	—	—	10	Hyperventilation
Present study					
Bertolet et al	100	6	23	8	Position
	100	3	10	2	Hyperventilation
	100	2	7	4	Valsalva

mal baseline. However, no ST-segment depression ≥1 mm was noted.

Our study demonstrates that ST-segment changes on AEM can be induced by position changes, hyperventilation or the Valsalva maneuver in almost one third of patients chosen for an electrocardiogram with a normal or near normal ST-segment baseline; however, ischemic-type ST-segment depression of 1 mm could be demonstrated in only 4%. ST-segment elevation ≥1 mm from an isoelectric baseline also was an infrequent occurrence. T-wave axis shifts of 180° were noted in 11% of patients after the physiologic maneuvers. Electrode shifts of 1 cm were more likely to induce ST-segment shifts from an abnormal baseline than from an isoelectric one; however, no ST-segment depression ≥1 mm was detected, regardless of the baseline.

This is the first study that examines the effects of various physiologic maneuvers on the electrocardiogram of cardiac patients as recorded by AEM. Deanfield et al[7] used AEM to screen for ischemic-type electrocardiographic changes after postural variations in 100 normal volunteers. There were no episodes of ST-segment depression ≥1 mm, only 1 episode of ST-segment elevation ≥1 mm, and 2 episodes of 180° T-wave axis shift. Some previous studies of cardiac patients using other detection methods are compared with the present study in Table II. In all, these past studies demonstrated ischemic-type ST-segment and T-wave changes in 0.3 and 1% of patients, respectively.

Screening for electrocardiographic changes induced by physiologic maneuvers is time- and labor-intensive for electrocardiographic technicians. However, we believe this practice should continue, because the results obtained may have an important role in the interpretation of ST-segment changes thought to be due to myocardial ischemia. Many of our patients manifested some ST-segment or T-wave changes during physiologic activities, which increased when the baseline was abnormal. These ST-segment and T-wave shifts (which alone may be insignificant) may be additive to other stimuli causing minor electrocardiographic changes resulting in the incorrect interpretation of myocardial ischemia. If AEM is to be performed for the detection of ischemic ST-segment changes, care should be taken to exclude those subjects who develop ischemic-type but artifactual electrocardiographic changes merely with changes of position or misplacement of the lead.

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Differentiation of Ventricular Tachycardia from Ventricular Fibrillation Using Intraventricular Electrogram Morphology

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Implantable antitachycardia devices are now capable of providing "ramp" therapy including antitachycardia pacing and low- and high-energy cardioversion for sustained ventricular tachycardia (VT) in addition to defibrillation of ventricular fibrillation (VF).[1,2] Appropriate therapy, however, is dependent on correct identification of VT and VF. Because of variations in ventricular electrographic amplitude during VF, currently implanted devices are unable to consistently detect consecutive ventricular depolarizations during VF.[3] As a result, the rate criteria for VF detection may sometimes overlap with the rate criteria used for VT detection. Morphologic analysis of intracavitary ventricular electrograms using correlation waveform analysis has been demonstrated in previous studies to be effective in discriminating normal sinus

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This study was supported in part by Grants BCS-8909042 and EID-9023514 from the National Science Foundation, Washington, D.C. Manuscript received February 20, 1992; revised manuscript received and accepted April 20, 1992.

rhythm from VT, paroxysmal bundle branch block of supraventricular origin, and retrograde atrial activation.[4–7] Whether VF is distinguishable from sinus rhythm and VT with a similar method has not been determined. This study examined whether VT and VF can be distinguishable from sinus rhythm and from each other by correlation waveform analysis of intracavitary ventricular electrograms.

Twelve consecutive patients were evaluated while undergoing routine cardiac electrophysiologic studies. Distal bipolar (1 to 500 Hz) intraventricular electrograms were recorded from an electrode catheter positioned in the right ventricular apex during sinus rhythm, monomorphic VT induced by programmed electrical stimulation, and VF induced by programmed stimulation or alternating current. Ventricular electrograms were recorded on FM magnetic tape and digitized subsequently on a PC at a sampling rate of 1,000 Hz. The programs for digitizing and waveform analysis were written in C and assembly language. A digital differentiator was used to detect each of the individual intracardiac electrograms. A template was created from a 15-second passage of sinus rhythm for correlation waveform analysis of subsequent 15- to 30-second passages of sinus rhythm, VT and VF. Correlation waveform analysis was used as a statistical measure of the similarity or dissimilarity of the waveform under analysis with the sinus rhythm template. The correlation coefficient was defined as:

$$\rho = \frac{\sum_{i=1}^{i=N} (t_i - \bar{t})(s_i - \bar{s})}{\sqrt{\sum_{k=1}^{k=N} (t_k - \bar{t})^2} \sqrt{\sum_{k=1}^{k=N} (s_k - \bar{s})^2}}$$

where t_k = the template points, S_k = the signal points to be processed, $\bar{t}$ = the average value of the template points, $\bar{s}$ = the average value of the signal points, N = the number of points in the template, and ρ = the index of merit. The value of the correlation coefficient therefore fell between ±1 such that identical waveforms had a value +1, waveforms which were inverses of one another had a value of −1, and all other, dissimilar waveforms had values between +1 and −1. A patient-specific window was chosen during creation of the sinus rhythm template to include depolarization only and to exclude the potentially confounding repolarization injury current caused by the acute placement of the electrode catheters. This window size was imposed on all subsequently analyzed electrograms. The template was aligned with the trigger point of the electrogram under analysis, and then shifted a maximum of 10 ms in both directions in order to maximize the alignment of the 2 waveforms. The magnitude of the variance of cycle-to-cycle correlation waveform analysis was then used as a discriminant function for VT and VF.

Table I summarizes the results for all 12 patients. The types of electrograms analyzed are illustrated in Figures 1 and 2. The window sizes of the analyzed electrograms ranged from 52 to 106 ms. Mean correlation coefficient separated sinus rhythm from VT in 10 of 12

TABLE I Results of Correlation Waveform Analysis for Discriminating Ventricular Tachycardia from Ventricular Fibrillation

	Sinus Rhythm		VT		VF	
Pt. No.	Mean p Value	SD	Mean p Value	SD	Mean p Value	SD
1	0.986	0.008	0.852	0.115	0.714	0.221
2	0.987	0.006	0.836	0.072	0.355	0.348
3	0.995	0.003	−0.108	0.097	0.499	0.382
4	0.970	0.003	0.848	0.017	0.405	0.453
5	0.980	0.006	0.882	0.041	0.429	0.493
6	0.962	0.020	0.641	0.047	0.625	0.408
7	0.995	0.002	0.925	0.007	0.650	0.433
8	0.990	0.021	0.969	0.013	0.347	0.432
9	0.984	0.011	0.868	0.022	0.228	0.490
10	0.977	0.049	0.960	0.018	0.881	0.092
11	0.959	0.024	0.040	0.177	0.162	0.499
12	0.996	0.003	0.870	0.087	0.313	0.718

VF = ventricular fibrillation; VT = ventricular tachycardia.

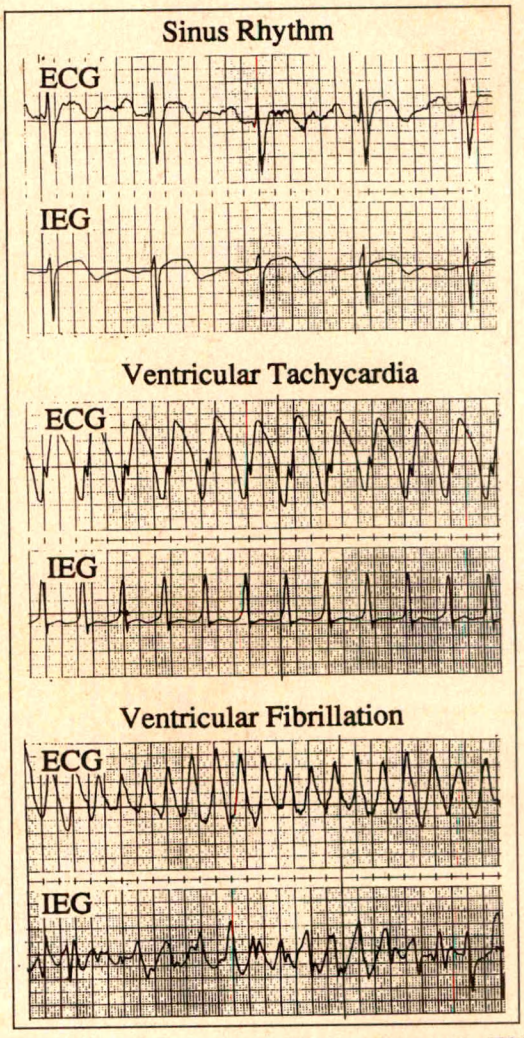


FIGURE 1. Examples of surface electrocardiographic (ECG) and distal bipolar intraventricular electrograms (IEG) of patient 11 during sinus rhythm, monomorphic ventricular tachycardia (VT) and ventricular fibrillation (VF). The difference in mean correlation coefficient from correlation waveform analysis of sinus rhythm (0.959) differentiated it from VT (0.040) and VF (0.162). The variance of VT (0.177)^2 differentiated it from VF (0.499)^2.

patients (83%) and sinus rhythm from VF in all 12 patients (100%). The range (and means) for standard deviation(s) were 0.004 to 0.049 (0.013) for sinus rhythm, 0.007 to 0.177 (0.059) for VT, and 0.092 to 0.718 (0.414) for VF. For each of the 12 patients, the individual variances for VT and VF were significantly different (F test, p <0.0001). A threshold midway between the average variance in VT and VF, respectively, was a successful discriminant in 11 of 12 patients (92%).

The primary method for tachycardia detection of VT and VF by currently implanted devices has been based on timing information derived from heart rate, including an abrupt increase in heart rate, detection of a rate that exceeds an arbitrary minimum, and observation of a stable RR interval during the tachycardia.[8] However, such algorithms lack specificity for VT and VF recognition.

The complementary use of time and frequency domain analysis has been proposed for VT and VF detection.[4–7,10–14] The only method now used in implanted devices for VF detection — probability density function[9] — has had limited applicability for patients who experience both recurrent VT and VF. Previous studies have demonstrated the efficacy of correlation waveform analysis in detecting VT when compared with other proposed time and frequency domain analyses of individual bipolar intraventricular electrograms.[4–7] The results of this study suggest that a similar time domain analysis of intraventricular bipolar electrograms may also be useful in discriminating VF from sinus rhythm as well as from more organized and more stable monomorphic VT.

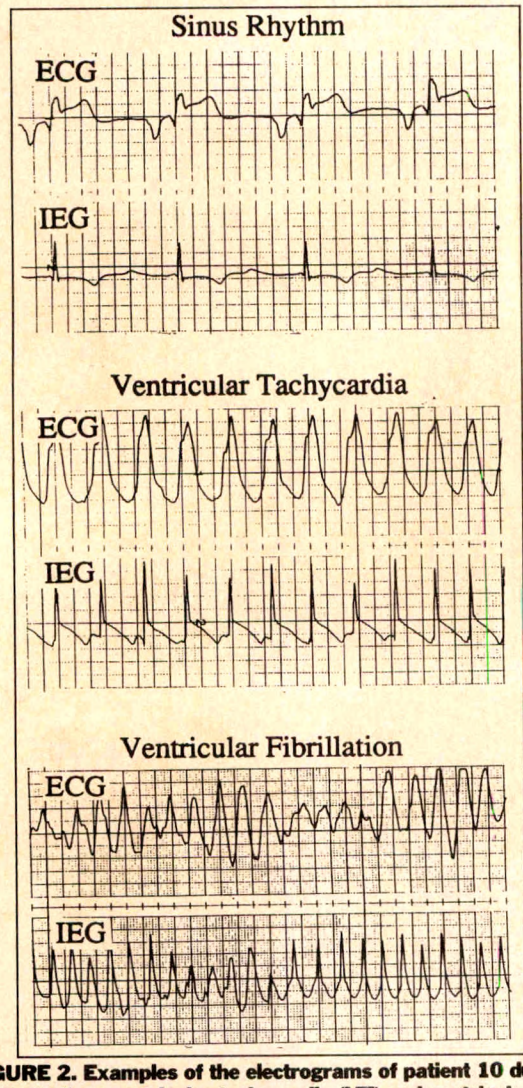


FIGURE 2. Examples of the electrograms of patient 10 during sinus rhythm, ventricular tachycardia (VT) and ventricular fibrillation (VF). The difference in mean correlation coefficient from correlation waveform analysis of sinus rhythm (0.977) differentiated it from VT (0.960) and VF (0.881). However, the variance of VT $(0.018)^2$ and VF $(0.092)^2$ were similar. Discrimination between these 2 tachyarrhythmias was not possible using this criterion. Abbreviations as in Figure 1.

The present study had several limitations. The recordings analyzed were from supine patients during clinical electrophysiologic studies. No effort was made to optimize any filter characteristics to improve alignment. The impacts of changes in position, hydration and vascular tone were not examined. Changes in electrogram amplitude that might occur during everyday activity of a patient with a permanent lead also remain unknown.

Although correlation waveform analysis has the potential advantages of being independent of electrogram amplitude and baseline fluctuations, its incorporation in currently available, implantable microprocessors may prove to be impractical because of its computational demands. Further work is necessary to determine whether other, less computationally demanding time domain methods are similarly effective in detecting and distinguishing VT and VF.[15]

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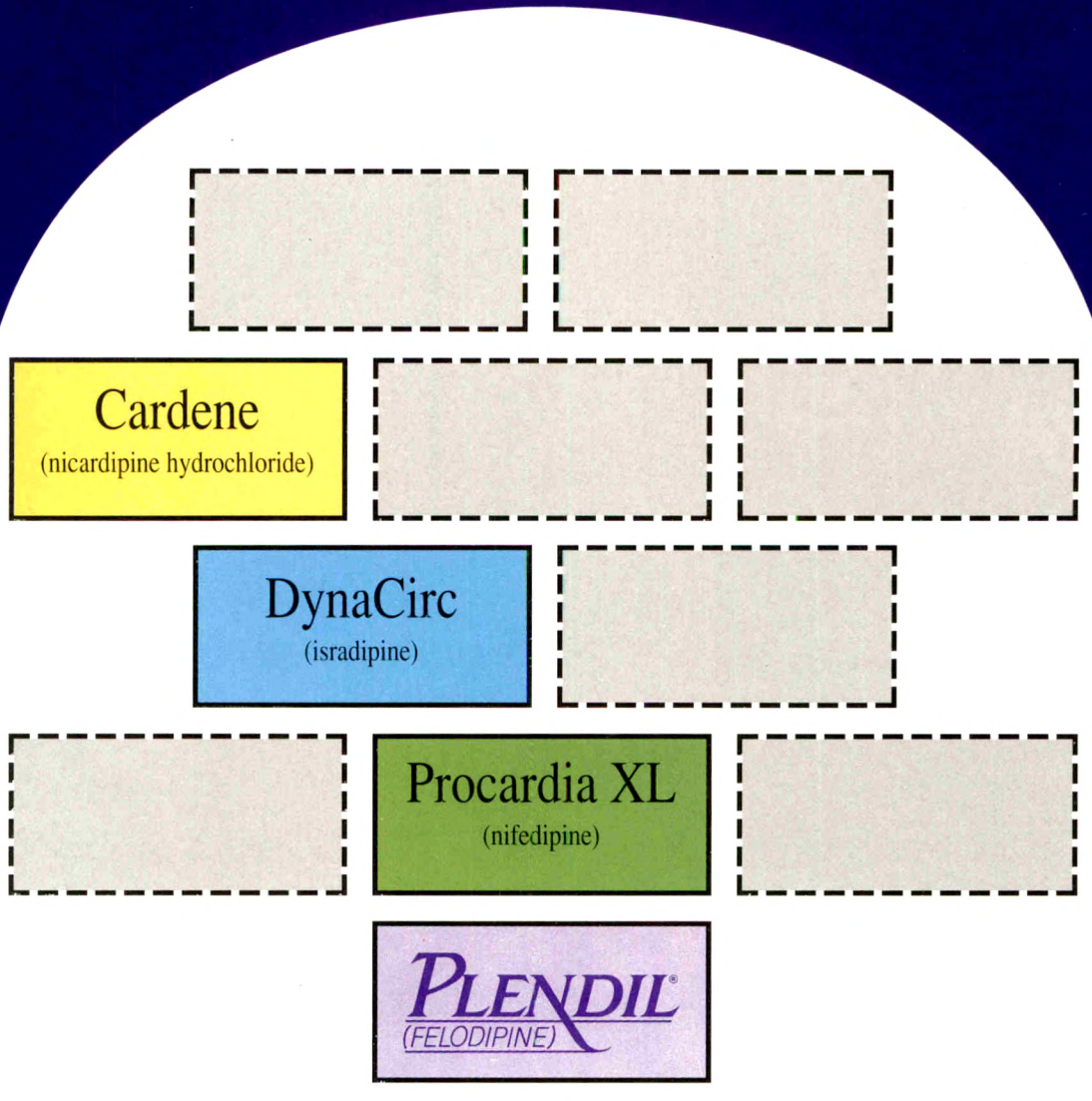
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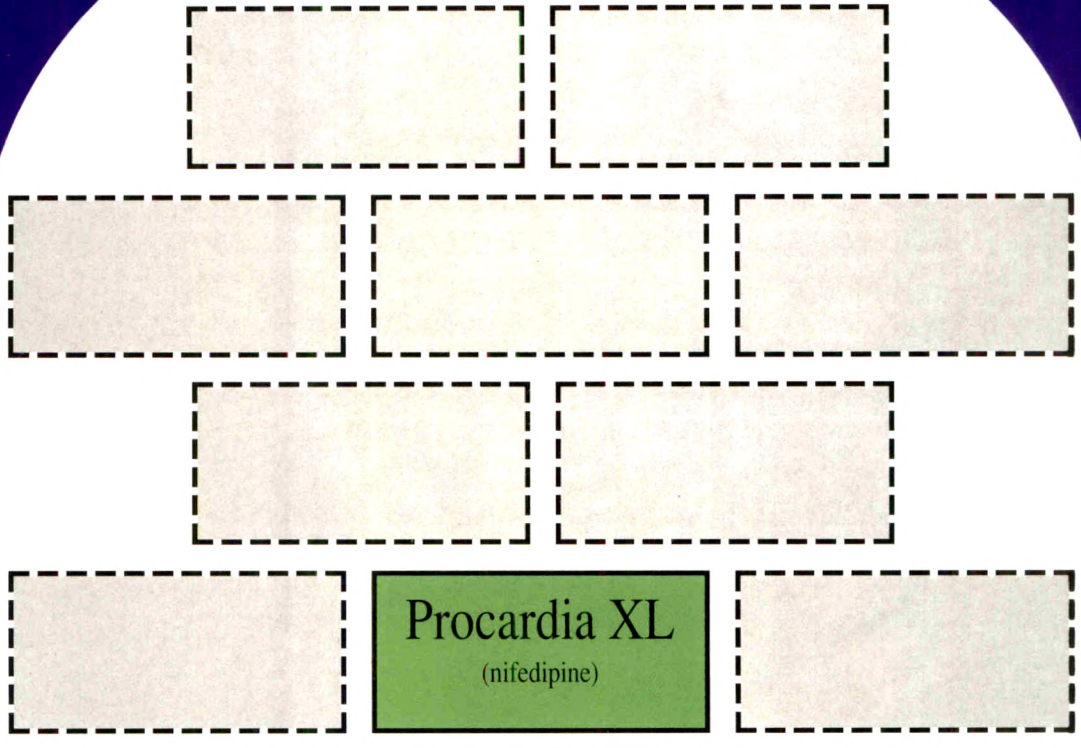
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Heart Failure: Although acute hemodynamic studies in a small number of patients with NYHA Class II or III heart failure treated with felodipine have not demonstrated negative inotropic effects, safety in patients with heart failure has not been established. Caution therefore should be exercised when using PLENDIL in patients with heart failure or compromised ventricular function, particularly in combination with a beta blocker.

Elderly Patients or Patients with Impaired Liver Function: Patients over 65 years of age or patients with impaired liver function may have elevated plasma concentrations of felodipine and may therefore respond to lower doses of PLENDIL. These patients should have their blood pressure monitored closely during dosage adjustment of PLENDIL and should rarely require doses above 10 mg. (See CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION.)

Peripheral Edema: Peripheral edema, generally mild and not associated with generalized fluid retention, was the most common adverse event in the clinical trials. The incidence of peripheral edema was both dose- and age-dependent. Frequency of peripheral edema ranged from about 10 percent in patients under 50 years of age taking 5 mg daily to about 30 percent in those over 60 years of age taking 20 mg daily. This adverse effect generally occurs within 2-3 weeks of the initiation of treatment.

Information for Patients: Patients should be instructed to take PLENDIL whole and not to crush or chew the tablets. They should be told that mild gingival hyperplasia (gum swelling) has been reported. Good dental hygiene decreases its incidence and severity.

NOTE: As with many other drugs, certain advice to patients being treated with PLENDIL is warranted. This information is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects.

Drug Interactions: ***Beta-Blocking Agents:*** A pharmacokinetic study of felodipine in conjunction with metoprolol demonstrated no significant effects on the pharmacokinetics of felodipine. The AUC and C_{max} of metoprolol, however, were increased approximately 31 and 38 percent, respectively. In controlled clinical trials, however, beta-blockers including metoprolol were concurrently administered with felodipine and were well tolerated.

Cimetidine: In healthy subjects pharmacokinetic studies showed an approximately 50 percent increase in the area under the plasma concentration time curve (AUC) as well as the C_{max} of felodipine when given concomitantly with cimetidine. It is anticipated that a clinically significant interaction may occur in some hypertensive patients. Therefore, it is recommended that low doses of PLENDIL be used when given concomitantly with cimetidine.

Digoxin: When given concomitantly with felodipine the peak plasma concentration of digoxin was significantly increased. There was, however, no significant change in the AUC of digoxin.

Other Concomitant Therapy: In healthy subjects there were no clinically significant interactions when felodipine was given concomitantly with indomethacin or spironolactone.

Interaction with Food: See CLINICAL PHARMACOLOGY, *Pharmacokinetics and Metabolism*.

Carcinogenesis, Mutagenesis, Impairment of Fertility: In a two-year carcinogenicity study in rats fed felodipine at doses of 7.7, 23.1 or 69.3 mg/kg/day (up to 28 times* the maximum recommended human dose on a mg/m² basis), a dose-related increase in the incidence of benign interstitial cell tumors of the testes (Leydig cell tumors) was observed in treated male rats. These tumors were not observed in a similar study in mice at doses up to 138.6 mg/kg/day (28* times the maximum recommended human dose on a mg/m² basis). Felodipine, at the doses employed in the two-year rat study, has been shown to lower testicular testosterone and to produce a corresponding increase in serum luteinizing hormone in rats. The Leydig cell tumor development is possibly secondary to these hormonal effects which have not been observed in man.

In this same rat study a dose-related increase in the incidence of focal squamous cell hyperplasia compared to control was observed in the esophageal groove of male and female rats in all dose groups. No other drug-related esophageal or gastric pathology was observed in the rats or with chronic administration in mice and dogs. The latter species, like man, has no anatomical structure comparable to the esophageal groove.

Felodipine was not carcinogenic when fed to mice at doses of up to 138.6 mg/kg/day (28 times* the maximum recommended human dose on a mg/m² basis) for periods of up to 80 weeks in males and 99 weeks in females.

Felodipine did not display any mutagenic activity *in vitro* in the Ames microbial mutagenicity test or in the mouse lymphoma forward mutation assay. No clastogenic potential was seen *in vivo* in the mouse micronucleus test at oral doses up to 2500 mg/kg (506 times* the maximum recommended human dose on a mg/m² basis) or *in vitro* in a human lymphocyte chromosome aberration assay.

A fertility study in which male and female rats were administered doses of 3.8, 9.6 or 26.9 mg/kg/day showed no significant effect of felodipine on reproductive performance.

Pregnancy: ***Pregnancy Category C:*** *Teratogenic Effects*: Studies in pregnant rabbits administered doses of 0.46, 1.2, 2.3 and 4.6 mg/kg/day (from 0.4 to 4 times* the maximum recommended human dose on a mg/m² basis) showed digital anomalies consisting of reduction in size and degree of ossification of the terminal phalanges in the fetuses. The frequency and severity of the changes appeared dose-related and were noted even at the lowest dose. These changes have been shown to occur with other members of the dihydropyridine class and are possibly a result of compromised uterine blood flow. Similar fetal anomalies were not observed in rats given felodipine.

In a teratology study in cynomolgus monkeys no reduction in the size of the terminal phalanges was observed but an abnormal position of the distal phalanges was noted in about 40 percent of the fetuses.

Nonteratogenic Effects: A prolongation of parturition with difficult labor and an increased frequency of fetal and early postnatal deaths were observed in rats administered doses of 9.6 mg/kg/day (4 times* the maximum human dose on a mg/m² basis) and above.

Significant enlargement of the mammary glands in excess of the normal enlargement for pregnant rabbits was found with doses greater than or equal to 1.2 mg/kg/day (equal to the maximum human dose on a mg/m² basis). This effect occurred only in pregnant rabbits and regressed during lactation. Similar changes in the mammary glands were not observed in rats or monkeys.

There are no adequate and well-controlled studies in pregnant women. If felodipine is used during pregnancy, or if the patient becomes pregnant while taking this drug, she should be apprised of the potential hazard to the fetus, possible digital anomalies of the infant, and the potential effects of felodipine on labor and delivery, and on the mammary glands of pregnant females.

Nursing Mothers: It is not known whether this drug is secreted in human milk and because of the potential for serious adverse reactions from felodipine in the infant, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: In controlled studies in the United States and overseas approximately 3000 patients were treated with felodipine as either the extended-release or the immediate-release formulation.

The most common clinical adverse experiences reported with PLENDIL® (Felodipine, MSD) administered as monotherapy in all settings and with all dosage forms of felodipine were peripheral edema and headache. Peripheral edema was generally mild, but it was age- and dose-related and resulted in discontinuation of therapy in about 4 percent of the enrolled patients. Discontinuation of therapy due to any clinical adverse experience occurred in about 9 percent of the patients receiving PLENDIL, principally for peripheral edema, headache, or flushing.

Adverse experiences that occurred with an incidence of 1.5 percent or greater during monotherapy with PLENDIL without regard to causality are compared to placebo in the table below.

Percent of Patients with Adverse Effects in Controlled Trials of PLENDIL as Monotherapy (Incidence of discontinuations shown in parentheses)

Adverse Effect	PLENDIL % N = 730	Placebo % N = 283
Peripheral Edema	22.3 (4.2)	3.5
Headache	18.6 (2.1)	10.6
Flushing	6.4 (1.0)	1.1
Dizziness	5.8 (0.8)	3.2
Upper Respiratory Infection	5.5 (0.1)	1.1
Asthenia	4.7 (0.1)	2.8
Cough	2.9 (0.0)	0.4
Paresthesia	2.5 (0.1)	1.8
Dyspepsia	2.3 (0.0)	1.4
Chest Pain	2.1 (0.1)	1.4
Nausea	1.9 (0.8)	1.1
Muscle Cramps	1.9 (0.0)	1.1
Palpitation	1.8 (0.5)	2.5
Abdominal Pain	1.8 (0.3)	1.1
Constipation	1.6 (0.1)	1.1
Diarrhea	1.6 (0.1)	1.1
Pharyngitis	1.6 (0.0)	0.4
Rhinorrhea	1.6 (0.0)	0.0
Back Pain	1.6 (0.0)	1.1
Rash	1.5 (0.1)	1.1

*Based on patient weight of 50 kg

In the two dose response studies using PLENDIL® (Felodipine, MSD) as monotherapy, the following table describes the incidence (percent) of adverse experiences that were dose-related:

Adverse Effect	Placebo N = 121	5.0 mg N = 72	10.0 mg N = 123	20 mg N = 50
Peripheral Edema	2.5	13.9	19.5	36.0
Palpitation	0.8	0.0	2.4	12.0
Headache	12.4	11.1	18.7	28.0
Flushing	0.0	2.8	8.1	20.0

In addition, adverse experiences that occurred in 0.5 up to 1.5 percent of patients who received PLENDIL in all controlled clinical studies (listed in order of decreasing severity within each category) and serious adverse events that occurred at a lower rate or were found during marketing experience (those lower rate events are in italics) were: *Body as a Whole:* Facial edema, warm sensation; *Cardiovascular:* Tachycardia, *myocardial infarction, hypotension, syncope, angina pectoris*, arrhythmia; *Digestive:* Vomiting, dry mouth, flatulence; *Hematologic: Anemia*; *Musculoskeletal:* Arthralgia, arm pain, knee pain, leg pain, foot pain, hip pain, myalgia; *Nervous/Psychiatric:* Depression, anxiety disorders, insomnia, irritability, nervousness, somnolence; *Respiratory:* Bronchitis, influenza, sinusitis, dyspnea, epistaxis, respiratory infection, sneezing; *Skin:* Contusion, erythema, urticaria; *Urogenital:* Decreased libido, impotence, urinary frequency, urinary urgency, dysuria.

Felodipine, as an immediate release formulation, has also been studied as monotherapy in 680 patients with hypertension in U.S. and overseas controlled clinical studies. Other adverse experiences not listed above and with an incidence of 0.5 percent or greater include: *Body as a Whole:* Fatigue; *Digestive:* Gastrointestinal pain; *Musculoskeletal:* Arthritis, local weakness, neck pain, shoulder pain, ankle pain; *Nervous/Psychiatric:* Tremor; *Respiratory:* Rhinitis; *Skin:* Hyperhidrosis, pruritus; *Special Senses:* Blurred vision, tinnitus; *Urogenital:* Nocturia.

Gingival Hyperplasia: Gingival hyperplasia, usually mild, occurred in <0.5 percent of patients in controlled studies. This condition may be avoided or may regress with improved dental hygiene. (See PRECAUTIONS, *Information for Patients*.)

Clinical Laboratory Test Findings: ***Serum Electrolytes:*** No significant effects on serum electrolytes were observed during short- and long-term therapy (see CLINICAL PHARMACOLOGY, *Renal/Endocrine Effects*).

Serum Glucose: No significant effects on fasting serum glucose were observed in patients treated with PLENDIL in the U.S. controlled study.

Liver Enzymes: One of two episodes of elevated serum transaminases decreased once drug was discontinued in clinical studies; no follow-up was available for the other patient.

OVERDOSAGE: Oral doses of 240 mg/kg and 264 mg/kg in male and female mice, respectively, and 2390 mg/kg and 2250 mg/kg in male and female rats, respectively, caused significant lethality.

In a suicide attempt, one patient took 150 mg felodipine together with 15 tablets each of atenolol and spironolactone and 20 tablets of nitrazepam. The patient's blood pressure and heart rate were normal on admission to hospital; he subsequently recovered without significant sequelae.

Overdosage might be expected to cause excessive peripheral vasodilation with marked hypotension and possibly bradycardia.

If severe hypotension occurs, symptomatic treatment should be instituted. The patient should be placed supine with the legs elevated. The administration of intravenous fluids may be useful to treat hypotension due to overdosage with calcium antagonists. In case of accompanying bradycardia, atropine (0.5-1 mg) should be administered intravenously. Sympathomimetic drugs may also be given if the physician feels they are warranted.

It has not been established whether felodipine can be removed from the circulation by hemodialysis.

DOSAGE AND ADMINISTRATION: The recommended initial dose is 5 mg once a day. Therapy should be adjusted individually according to patient response, generally at intervals of not less than two weeks. The usual dosage range is 5-10 mg once daily. The maximum recommended daily dose is 20 mg once a day. That dose in clinical trials showed an increased blood pressure response but a large increase in the rate of peripheral edema and other vasodilatory adverse events (see ADVERSE REACTIONS). Modification of the recommended dosage is usually not required in patients with renal impairment.

PLENDIL should be swallowed whole and not crushed or chewed.

Use in the Elderly or Patients with Impaired Liver Function: Patients over 65 years of age or patients with impaired liver function, because they may develop higher plasma concentrations of felodipine, should have their blood pressure monitored closely during dosage adjustment (see PRECAUTIONS). In general, doses above 10 mg should not be considered in these patients.

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Effects of Severe Pulmonary Hypertension on Outcome of Balloon Mitral Valvotomy

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Severe pulmonary hypertension is no longer considered a major risk factor for patients undergoing surgical treatment of mitral stenosis.[1] Whereas balloon mitral valvotomy (BMV) has recently gained favor as an alternative to the surgical treatment of patients with uncomplicated, pliable mitral stenosis,[2] the safety and efficacy of BMV in patients with severe pulmonary hypertension has, to our knowledge, been addressed in only 1 study. From the experience at Beth Israel Hospital, Levine et al[3] reported excellent immediate results and a low incidence of complications of BMV in 14 patients with moderate to severe pulmonary hypertension. Nevertheless, during our early BMV experience, we approached this subset of patients with trepidation for several reasons: (1) because of their more precarious hemodynamic status, they may be less tolerant of the stress of the procedure; (2) the transseptal puncture may be more difficult because of large right-sided chambers; and (3) because of tighter mitral stenosis, the valve may be more difficult to cross or more susceptible to tearing. This paper reports our BMV results in 52 such patients with severe pulmonary hypertension (mean pulmonary artery pressure ≥50 mm Hg).

From among 179 patients who underwent BMV at our hospital between June 1989 and January 1992, we identified, retrospectively, 52 who had severe pulmonary hypertension defined arbitrarily as a mean pulmonary artery pressure ≥50 mm Hg measured at catheterization just before BMV. All patients were treated with a loop diuretic, a β blocker, or both, before BMV.

Two-dimensional echocardiographic examination was performed on each patient at the same admission during which the procedure was performed using a Hewlett-Packard Sonos imaging system attached to either a 2.5 or 5 MHz transducer. The mitral valve and subvalvular apparatus were examined in multiple views. All examinations were recorded on tape for later playback and analysis. Mitral valves were graded using the 0 to 4 point system of Abascal et al[4] for each of 4 anatomic parameters: valve mobility, thickness, calcification and subvalvular disease. For the present analysis, a minimum score of 1 was given if mobility was impaired only at the leaflet tips, if thickness was near normal, and if there was minimal thickening of the chordae just below the valve; a score of 0 was given if no calcium was identified. Thus, the ideal valve was given a score of 3 and the worst possible score was 16.

The technique of catheterization has been described previously.[5] Patients were premedicated with promethazine 25 mg and meperidine 25 mg intramuscularly, and were given heparin after the transseptal puncture. Left ventricular pressure was measured with either a pigtail micromanometer catheter balanced to a fluid-filled transducer or, in the minority of cases, a standard fluid-filled pigtail catheter. Left atrial pressure was measured with a well flushed 8Fr USCI transseptal sheath. Cardiac output was measured by thermodilution. The transmitral gradient was measured by digitizing the pressures with a computer and digitizing tablet. Mitral valve areas reported both before and after BMV were computed with the Gorlin formula. Pulmonary vascular resistance was computed as (mean pulmonary artery − mean left atrial pressure) × 80/cardiac output. BMV was accomplished with a single (25 mm, n = 4) or double (n = 21) Mansfield balloon or, when it became available to us, an Inoue balloon (Toray Medical Company, LTD, Tokyo, Japan) in 26 patients (in 1 additional patient in whom an Inoue balloon was used, a single attempt at BMV failed). The summed balloon diameter was taken as the simple sum of the 2 fully inflated balloon diameters when 2 Mansfield balloons were used. A 1.5:1 atrial shunt by oximetry was regarded as significant using superior ± inferior vena cava samples as mixed venous blood (measured after withdrawal of the balloon from the septostomy in most patients). Mitral regurgitation was graded on a scale of 0 to 4. Intermediate grades were sometimes used (e.g., 1.5+ when there was faint opacification of the entire atrium during systole which cleared during diastole).

Statistical analysis was performed using paired t *tests for continuous paired variables. Nonparametric tests were used for unpaired and categorical variables.*

BMV using the double Mansfield balloon technique initially failed in 1 patient (4%), but a subsequent attempt at BMV with an Inoue balloon was successful. In 4 patients (15%), an Inoue balloon could not be passed across the mitral valve on the first attempt; of these 4, BMV was successfully performed with a single Mansfield balloon during the same procedure in 1, and during a second procedure using an Inoue balloon in 2. Thus, the procedure was ultimately completed in 98% of the 52 patients.

There were no instances of tamponade, embolization or cardiac arrest. An increase in mitral regurgitation grade of >1 (out of 4) after BMV was observed in 16 patients (31%), and the hemodynamic results for these 16 (group 2) are listed in Table I separately from those in whom no significant increase mitral regurgitation occurred (group 1). None of the measured baseline hemodynamic parameters were significantly different between the 2 groups, nor was there any difference in age, functional class, rhythm or valve score between group 1 and group 2 (Table II). However, there were fewer Inoue balloons used (i.e., more Mansfield balloons) and the

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TABLE I Results for Completed Balloon Mitral Valvotomies (n = 51) by Group (with and without mitral regurgitation)

	Group 1 (n = 35)		Group 2 (n = 16)	
	Before	After	Before	After
Pulmonary artery systolic (mm Hg)	89 ± 14	63 ± 14	93 ± 15	68 ± 25
Pulmonary artery diastolic (mm Hg)	44 ± 7	30 ± 8	45 ± 8	33 ± 14
Pulmonary artery mean (mm Hg)	60 ± 8	41 ± 10	62 ± 10	44 ± 18
Left atrial mean (mm Hg)	22 ± 5	15 ± 6	25 ± 6	21 ± 7
Mitral valve gradient (mm Hg)	15 ± 4	5 ± 2	15 ± 4	7 ± 4
Cardiac output (liters/min)	3.2 ± 0.7	3.6 ± 0.9	3.3 ± 0.9	3.1 ± 0.7
Mitral valve area (cm^2)	0.71 ± 0.16	1.73 ± 0.71	0.71 ± 0.24	—
Pulmonary vascular resistance (dynes s cm^{-5})	984 ± 363	623 ± 280	1,026 ± 670	620 ± 368
Mitral regurgitation grade (0–4)	0.5 ± 0.7	0.8 ± 0.8	0.4 ± 0.6	2.9 ± 0.9
Atrial shunt detected		8 (23%)		2 (13%)

TABLE II Clinical, Procedural and Anatomic Differences Between the Two Groups

	Group 1 (n = 35)	Group 2 (n = 16)
Age (years)	23 ± 9	28 ± 11
Men:women	15:20	2:14
Inoue balloons	22 (63%)	4 (25%)*
Summed balloon diameter:body surface area (mm/m^2)	22 ± 5	25 ± 4*
NYHA functional class	3.0 ± 0.4	2.8 ± 0.6
Normal sinus rhythm	33 (94%)	15 (94%)
Valve score (0–16)	6.4 ± 1.9	6.6 ± 2.0
Mobility (1–4)	1.4 ± 0.5	1.5 ± 0.5
Thickness (1–4)	1.5 ± 0.5	1.7 ± 0.5
Calcium (0–4)	1.0 ± 0.9	1.3 ± 1.0
Subvalvular (1–4)	2.5 ± 0.7	2.2 ± 0.8

Only the frequency of use of Inoue balloons and the ratio of summed balloon diameter:body surface area were significantly different (p = 0.03) between groups.
NYHA = New York Heart Association.

summed balloon diameter:body surface area ratio was larger in group 2.

No patient in group 2 required urgent mitral valve surgery, but 2 underwent elective mitral valve replacement. Two patients in group 1 underwent elective mitral valve surgery for inadequate BMV results.

Levine and co-workers[3] previously demonstrated the feasibility of BMV in the presence of moderate to severe pulmonary hypertension in 14 patients with mitral stenosis and a mean pulmonary artery pressure >40 mm Hg (group mean pressure 51 mm Hg, mean resistance 630 dynes s cm^{-5}). Furthermore, despite the advanced age (mean 63 years) and presence of "extensive mitral valve calcification" in all patients, hemodynamic results were favorable (valve area 0.7 to 1.6 cm^2 immediately after BMV, 1.3 cm^2 at 7 ± 4 month follow-up) with little increase in mitral regurgitation grade. However, because this small group of patients differs in age and valve morphology from our population, we initially attempted BMV in the presence of severe pulmonary hypertension with some trepidation for reasons previously stated, and believe it worthwhile to examine our results retrospectively in a larger group of patients.

Despite the potential for technical difficulty in patients with increased pulmonary artery pressures, there were no procedural complications (i.e., perforation, embolization, hemodynamic collapse) and there was only 1 patient in whom BMV could not ultimately be accomplished. Difficulty was more often encountered passing an Inoue balloon than passing the Mansfield balloon across the mitral valve, but overall, we and other investigators[6] found BMV to be simpler and quicker with the Inoue compared with the double-balloon technique. Although we have not compared the incidence of mitral regurgitation with these 2 balloon techniques in our total series of patients, the Inoue balloon was used more often in the group without new mitral regurgitation than in group 2. Thus, the summed balloon diameter was larger in group 2 in which the 2-balloon Mansfield technique was more often used, and is corroborated by the data on balloon diameter in Table II.

The frequency of significant (>1 + increase) mitral regurgitation after BMV in this study is somewhat higher than in most other reports.[3–4,6,8,9] We did not compare the frequency of mitral regurgitation in this cohort with that of the rest of our population, but it is higher than in a previously reported cohort.[7] If the incidence of mitral regurgitation is somewhat higher in the presence of pulmonary hypertension, the cause is not obvious. None of the valve scores differed between groups 1 and 2, nor did the severity of stenosis. Although a direct comparison is not possible, it does appear that, although our total valve scores were lower than in other series,[4,8] the extent of subvalvular disease may have been slightly greater; according to other workers,[9] this could increase the likelihood of mitral regurgitation after BMV. Despite the relatively high incidence of mitral regurgitation, the overall hemodynamic results were good, with a decline in valve gradient and pulmonary artery pressure occurring even in group 2.

In conclusion, BMV can be both safe and effective in severe pulmonary hypertension, but approximately one-third of the patients develop an increase in mitral regurgitation.

Acknowledgment: We would like to acknowledge John Barlow, MD, for his thoughtful comments which helped motivate us to perform this study, and for reviewing the manuscript.

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Relation of Exercise Capacity in Dilated Cardiomyopathy to Left Atrial Size and Systolic Function

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There is evidence to suggest that abnormalities of left ventricular diastolic function rather than systolic function may be the most important determinants of the effort tolerance of patients with chronic heart failure.[1] Because left atrial (LA) function is closely related to left ventricular diastolic function, it was hypothesized that the exercise capacity of patients with dilated cardiomyopathy is related to LA size and systolic function. The present study was undertaken to test this hypothesis.

Fourteen patients with dilated cardiomyopathy were studied. The diagnosis of dilated cardiomyopathy was based on the following criteria: (1) angiographic left ventricular ejection fraction <0.40 and left ventricular end-systolic volume >100 cm^3; (2) no evidence of coronary artery disease in coronary arteriography; and (3) absence of valvular, congenital and hypertensive heart disease. Ten subjects with average life styles, no history of heart disease, normal resting electrocardiogram and M-mode, 2-dimensional and Doppler echocardiograms served as normal controls. All patients had been ambulatory and clinically stable for ≥3 months and had undergone >3 cardiopulmonary exercise tests before entry in the study. Medication consisted of oral diuretics (9 patients received 40 mg of furosemide once daily and 5 patients 40 mg twice daily) and digoxin in all patients; 9 patients additionally received angiotensin-converting enzyme inhibitors (6 patients received 12.5 mg of captopril twice daily and 3 patients 5 mg of enalapril once daily). No patient was treated with β blockers. Patients with atrial fibrillation (n = 3), significant (>1+ in angiography and Doppler echocardiography) mitral regurgitation (n = 3) and abnormalities of atrioventricular conduction necessitating pacemaker implantation (n = 1) were excluded.

LA and left ventricular volumes were echocardiographically (ATL Ultra Mark 9 imaging system equipped with a 3 MHz transducer) measured from the apical 4- and 2-chamber views, using the biplane area-length method.[2] LA maximal volume was measured at the point of mitral valve opening, and minimal volume at the point of mitral valve closure. LA volume at onset of atrial systole was considered the volume corresponding to the onset of the P wave in the simultaneously recorded electrocardiogram. Left ventricular end-diastolic volume was measured at the point of mitral valve closure and left ventricular end-systolic volume at the point of mitral valve opening. LA systolic function was evaluated with the LA active emptying fraction = (volume at onset of atrial systole − minimal volume)/volume at onset of atrial systole.[2] After echocardiography, cardiopulmonary exercise testing with continuous expired gas analysis (Minjhardt OX 4 gas analyzer) was performed on an electrically braked treadmill, according to Weber's protocol.[3] All patients had to stop exercise testing because of dyspnea or fatigue. No test was terminated for any other reason.

Values are presented as mean ± 1 SD. Statistical comparisons were performed using Student's t *test for unpaired data and linear regression analysis. A p value <0.05 was considered statistically significant.*

Demographic, cardiopulmonary exercise testing and echocardiographic data of the study cohort are listed in Table I. Exercise duration and peak oxygen consumption were decreased in patients with dilated cardiomyopathy compared with in control subjects. LA volumes (maximal, at onset of atrial systole, and minimal) were higher, and LA active emptying and left ventricular ejection fractions were significantly lower in dilated cardiomyopathy than in control subjects.

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TABLE I Demographic, Cardiopulmonary Exercise Testing and Echocardiographic Data of Study Group

	Age (yr)		Sex		Exercise Duration (sec)		$P\dot{V}O_2$ (ml/kg/min)		Vmax (cm^3)		Vp (cm^3)		Vmin (cm^3)		ACTEF		LVEF	
	NL	DC	NL	DC	NL	DC	NL	DC	NL	DC	NL	DC	NL	DC	NL	DC	NL	DC
	54	60	F	M	880	375	21	11	47	112	29	98	20	89	0.310	0.092	0.82	0.23
	68	23	M	M	950	415	24	12	54	123	33	110	20	105	0.394	0.045	0.51	0.19
	53	39	F	M	850	510	20	19	65	73	36	65	24	47	0.333	0.277	0.75	0.35
	49	57	M	M	920	545	25	18	45	62	24	48	16	37	0.333	0.229	0.68	0.36
	44	47	F	M	900	490	22	16	35	95	22	68	14	51	0.364	0.250	0.66	0.31
	34	45	F	M	800	865	21	18	31	33	18	25	12	15	0.333	0.400	0.70	0.32
	57	46	M	M	930	830	26	17	44	51	31	36	19	26	0.387	0.278	0.73	0.39
	58	60	M	F	850	415	23	13	63	60	38	51	24	37	0.368	0.275	0.73	0.30
	36	58	F	M	830	470	21	12	48	116	26	96	16	79	0.385	0.177	0.72	0.36
	65	63	M	M	860	385	23	14	32	83	20	65	10	51	0.500	0.215	0.67	0.22
		40		M		525		18		71		61		48		0.213		0.22
		56		M		605		15		75		60		47		0.217		0.19
		55		F		415		14		82		60		50		0.167		0.21
		51		M		425		13		80		54		48		0.111		0.22
Mean	51.8	50			877	519.3	22.6	15	46.4	79.7	27.7	64	17.5	52.1	0.37	0.21	0.70	0.28
SD	11.3	10.9			47.6	153.9	1.96	2.7	11.9	25.3	6.8	23.5	4.7	24	0.05	0.09	0.08	0.07
p value	⌊ NS ⌋				⌊0.0001⌋		⌊0.0001⌋		⌊0.0009⌋		⌊0.0001⌋		⌊0.0002⌋		⌊0.0001⌋		⌊0.0001⌋	

ACTEF = left atrial active emptying fraction; DC = dilated cardiomyopathy; LVEF = left ventricular ejection fraction; NL = normal control subjects; NS = not significant; $P\dot{V}O_2$ = peak exercise oxygen consumption; Vmax, Vp, Vmin = left atrial maximal, at onset of atrial systole and minimal volumes, respectively.

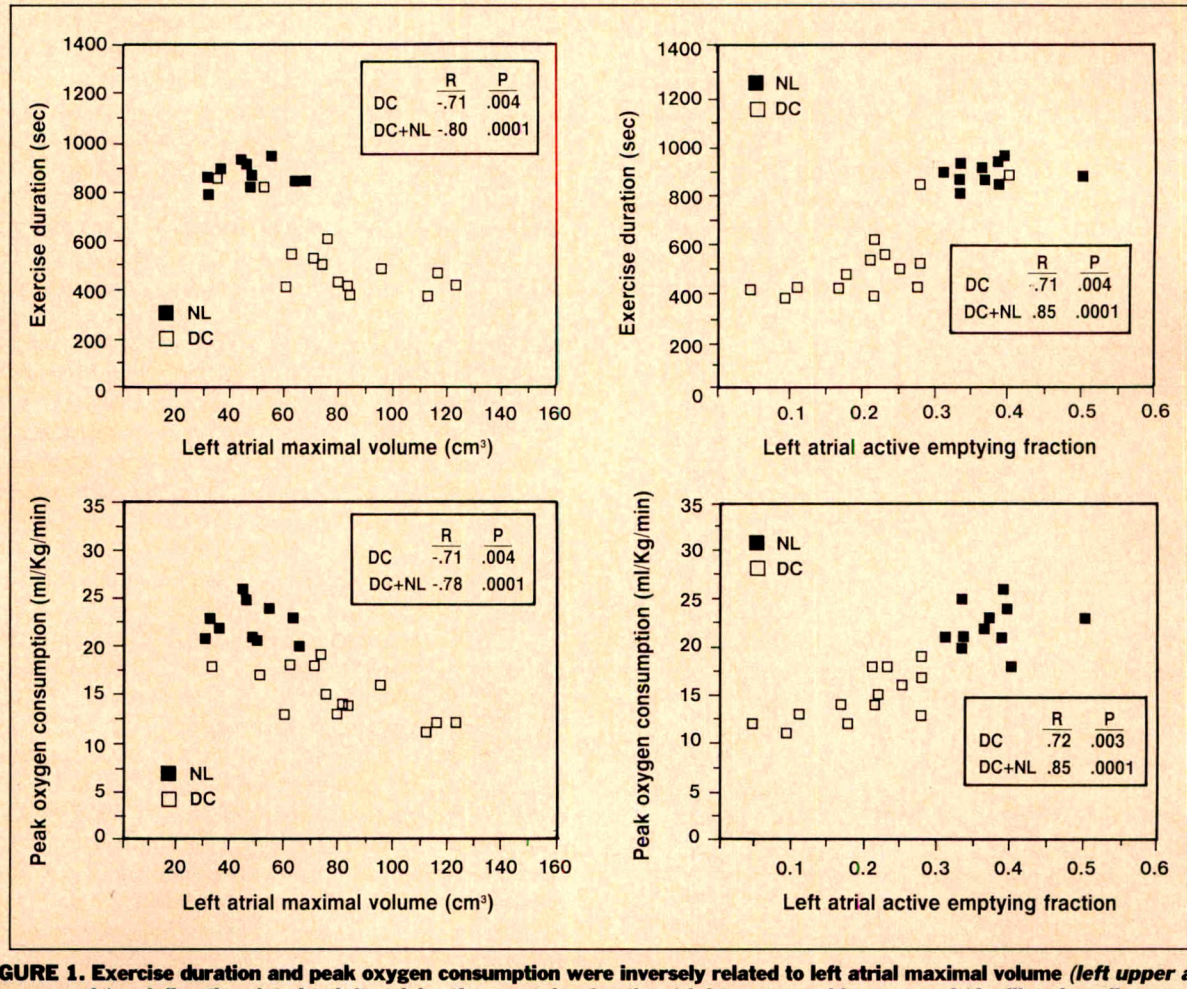


FIGURE 1. Exercise duration and peak oxygen consumption were inversely related to left atrial maximal volume *(left upper and lower panels)* and directly related to left atrial active emptying fraction *(right upper and lower panels)* in dilated cardiomyopathy (DC). Similar results were obtained when normal control subjects (NL) were included in analysis.

Figure 1 shows that exercise duration and peak oxygen consumption were inversely related to LA maximal volume and directly related to LA active emptying fraction in dilated cardiomyopathy, and that these correlations were maintained when control subjects were included. Exercise duration and peak oxygen consumption were poorly related to left ventricular ejection fraction in dilated cardiomyopathy ($r = 0.5$ [$p = 0.07$], and $r = 0.46$ [$p = 0.1$], respectively).

The findings of the present study indicate that in dilated cardiomyopathy, decreased exercise capacity is associated with increased LA size and reduced LA systolic function. Furthermore, they confirm the absence of a relation between left ventricular systolic function and exercise capacity in heart failure reported in previous studies.[4,5]

There are several explanations for the observed relation between exercise capacity and LA size and systolic function in dilated cardiomyopathy. Increased LA size may lead to progressive dysfunction of the baroreceptor reflex arcs that originate within the left atrium, resulting in increased neurohumoral activity and altered vascular reactivity.[6] Reduced LA systolic function may contribute to a decrease in left ventricular preload and stroke volume according to the Frank-Starling mechanism,[7] especially during exercise.[8] Furthermore, reduced LA systolic function may result in pulmonary venous hypertension and increased pulmonary vascular resistance, thereby limiting right ventricular output, left ventricular filling and systemic blood flow during exercise.[4]

In conclusion, increased LA size and reduced LA systolic function are predictors of decreased exercise capacity in dilated cardiomyopathy.

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Circadian Rhythm of Pulmonary Embolism in Patients with Acute Spinal Cord Injury

James H. Frisbie, MD, and G.V.R.K. Sharma, MD

Thrombotic events with a circadian rhythm have been described during the past several years, with onset of myocardial infarction and stroke predominating in the morning hours.[1,2] Recently, a circadian rhythm for pulmonary thromboembolism has been reported; the onset of these events also prevailed in the morning hours.[3] Patients with spinal cord injury are known to be at risk for pulmonary embolism during the early course of their paralysis.[4] Because all of the patients with acute spinal cord injury are a hospitalized population in whom the onset of pulmonary embolic events can be observed and documented, we examined the issue of a circadian rhythm for pulmonary embolism.

Over the 16-year period from 1974 to 1990, 13 patients, about 2% of the 600 initial admissions for spinal cord injury, sustained clinically significant pulmonary embolism. Embolism was documented by autopsy in 4, pulmonary angiography in 6, and perfusion and ventilation lung scanning that indicated large or multiple areas of mismatch in 3. The patients are described in Table I. Some patients sustained multiple embolic events (Table I). These were accepted as such if the event was consistent with the signs and symptoms of pulmonary embolism and without other explanation.[5]

The records were reviewed for the time of day, rounded to the nearest hour, in which an embolic event occurred. The timing of an event relative to the definitive diagnosis of pulmonary embolism was also noted.

The number of patients whose first event occurred between 12 midnight and 12 noon were compared with

TABLE I Description of Pulmonary Embolism Cases

Pt. No.	Age (yr) & Sex	Level of Paralysis	Prophylaxis	Onset of PE (days after paralysis)
1	26F	L1	LDH	81*
2	33M	T5	LDH	55, 55†
3	49M	T10		20
4	22M	C4		12
5	40M	L3	LDH	23, 23‡
6	39F	C4		18
7	28M	C6		7, 7‡
8	37M	L1	LDH	15
9	42M	T12		11
10	22M	C4		63, 63, 80, 81‡§
11	32M	C6	LDH	16‡
12	38M	L2		10
13	25M	L4	LDH	25

*Low-dose heparin stopped on day 57 after injury.
†Low-dose heparin stopped on day 52.
‡Deceased.
§Emboli recurred even during high-dose heparin administration.
LDH = low-dose heparin (5,000 U of sodium heparin subcutaneously every 12 or 8 hours); PE = pulmonary embolism.

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Manuscript received March 9, 1992; revised manuscript received April 28, 1992, and accepted May 1.

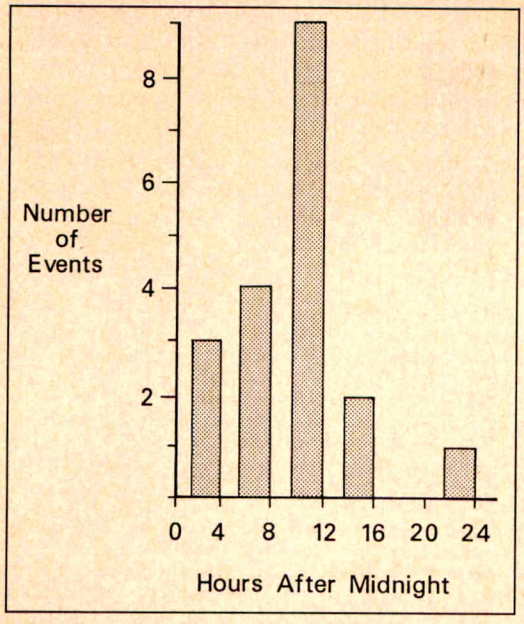


FIGURE 1. Each time represents the number of embolic events during the preceding 4 hours.

the number occurring in the remaining 12 hours, tested by the exact binomial distribution and expressed with 1-sided probability. The number of events occurring during each half of the day were tested in the same way.

The 13 subjects sustained 19 pulmonary embolic events. The events were dyspnea (5), cardiovascular collapse (5), chest pain (4), apprehension (2), hemoptysis (2) and syncope (1). The time between the last pulmonary embolic event and confirmatory diagnosis was <1 day in 12 subjects, and 4 days in the remaining subject. The number of subjects in whom the onset of pulmonary embolism occurred before noon was 11, $p = 0.01$. The number of pulmonary embolic events recorded before noon was 16, $p = 0.002$. The distribution of events by time of day is shown in Figure 1. Four patients in this series died, all between 12 midnight and 12 noon.

By chart review Colantonio et al[3] detected a circadian and seasonal rhythmicity in 152 cases of autopsy-proved pulmonary embolism, in which the hour and the month of the onset of pulmonary embolic could be determined. They found the highest incidence between 5 and 10 A.M. and in the winter season. The patient population was not specified. Our observations in patients with spinal cord injury described here confirm the Colantanio report of a circadian rhythm for pulmonary embolism.

Circadian mechanisms of pulmonary thromboembolism consist of 2 processes: (1) thrombus formation, usually in the deep venous system of the lower extremities; and (2) thrombus release, presumably generated by partial thrombolysis and fragmentation or by mechanical "triggers."

Thrombus formation in the morning hours, established for myocardial infarction and stroke,[1,2] is supported by evidence for increased platelet aggregability between 6 and 9 A.M.[6] Whether the venous thrombus develops at a similar time of day has not been established. However, a low endogenous plasminogen activator activity in the morning hours[7] favors thrombus formation or incomplete lysis. The venographic finding of dye tracking between the vein wall and the thrombus in deep vein thrombosis is indicative of incomplete lysis and separation of the thrombus from its moorings.[8]

Thrombus release by venospasm as an internal mechanical trigger can be suspected in patients with spinal cord injury because of their well-known autonomic instability and changes in vasomotor tone. Thrombus release by external mechanical triggers — turns made every 2 hours around the clock and passive exercise spaced at morning, noon and afternoon sessions — may have played a role in our patients: 5 embolic events occurred during or immediately after passive exercise to the lower extremities or turning the spinal cord-injured patient in bed.

Because a diagnosis of pulmonary embolism may be delayed or missed due to an atypical presentation, recognition of the predominant occurrence of this condition in the morning hours can raise the level of suspicion, leading to an early and accurate diagnosis.

The prophylaxis of pulmonary embolism was not uniformly successful in our patients. Three of the 4 deaths in our series occurred in patients who had been treated with a low-dose heparin regimen. Since a constant infusion of heparin has been shown to exert an effect in a circadian pattern with minimal anticoagulation at 7 A.M.,[9] awareness of the 12 midnight to 12 noon embolic risk can lead to a better timing of prophylaxis for pulmonary embolism.

Any further attempt to confirm the circadian rhythm of pulmonary embolism might address the limitations of this study and: (1) expand the number of subjects; (2) conduct the study prospectively; (3) consider other high-risk circumstances such as hip or abdominal surgery, stroke, heart failure and malignancy; and (4) determine the onset of venous thrombosis and the level of coagulability also by time of day.

In summary, a 12 midnight to 12 noon predominance of pulmonary embolism occurs in patients with acute spinal cord injury, an observation that may have diagnostic and therapeutic implications in the management of this and other high risk populations.

Acknowledgment: We thank Roger Davis of the Harvard School of Public Health for his statistical review.

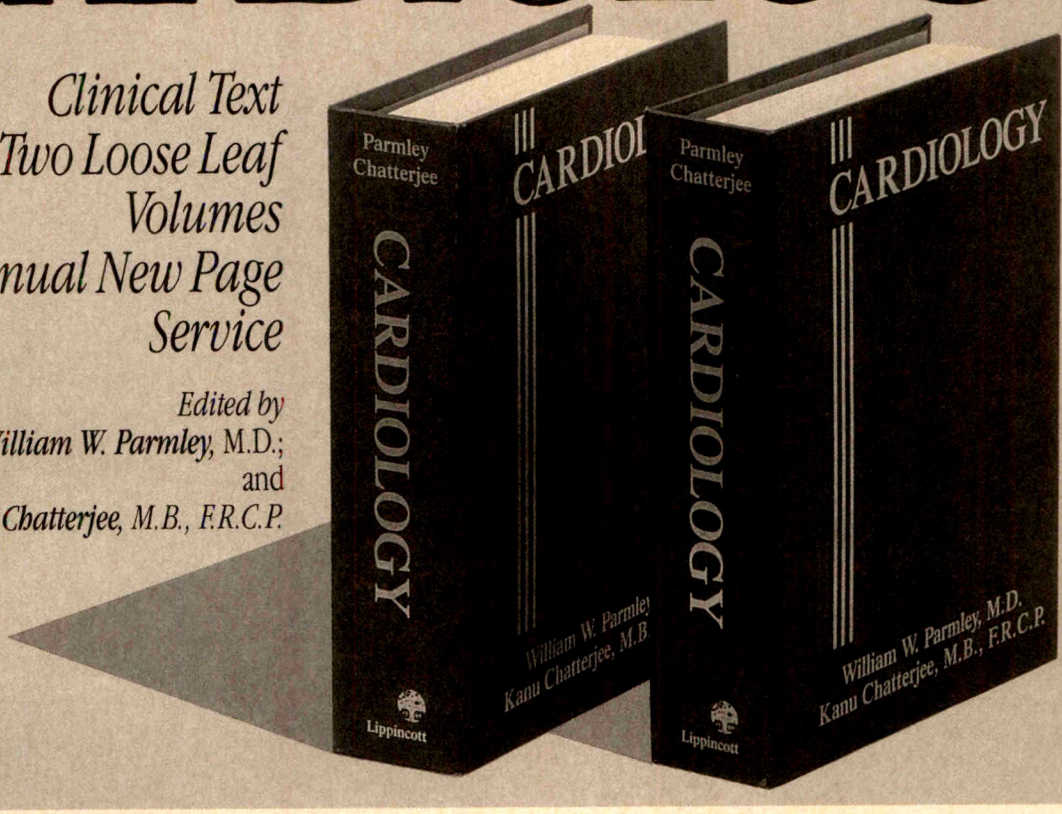
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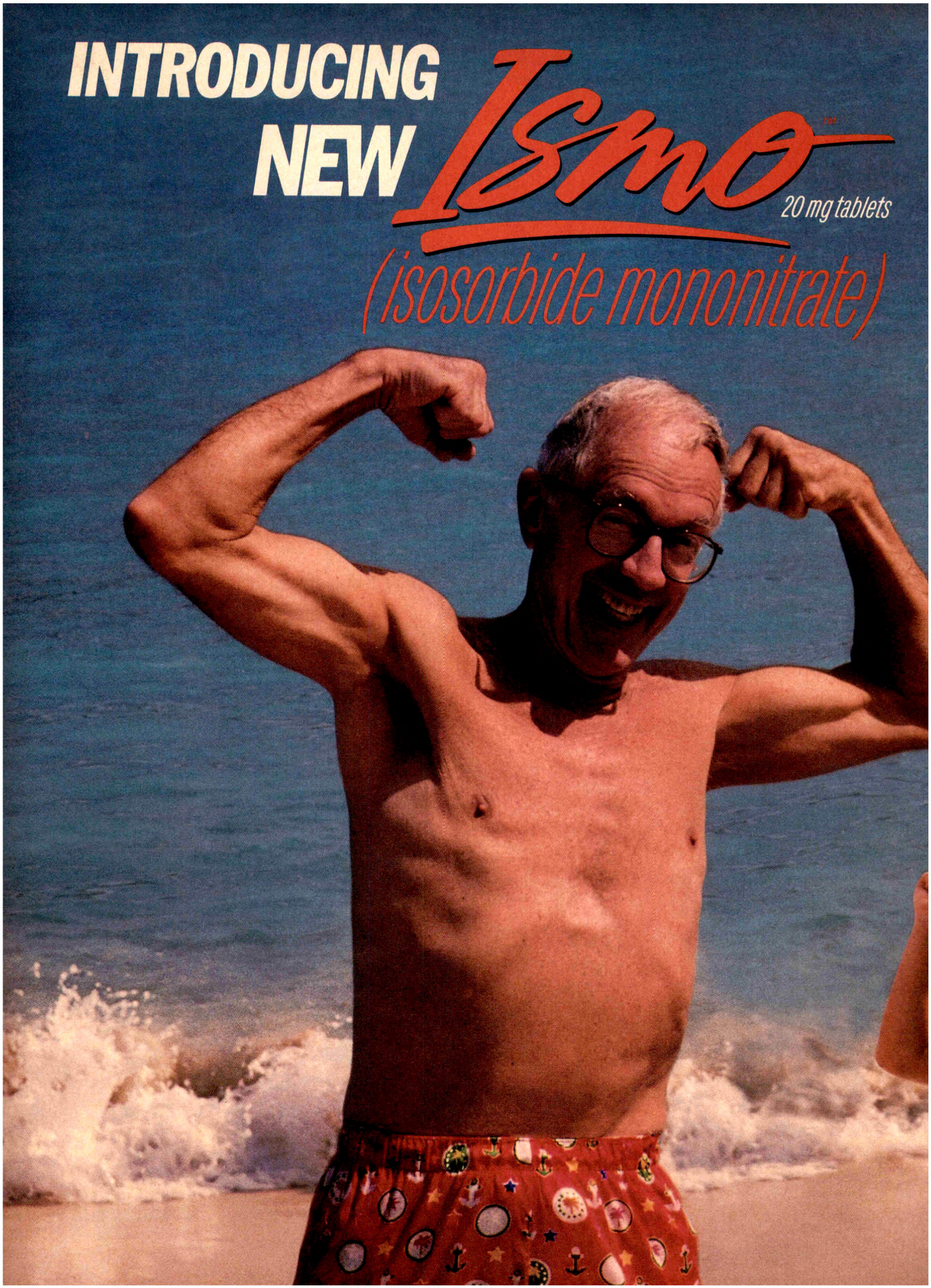
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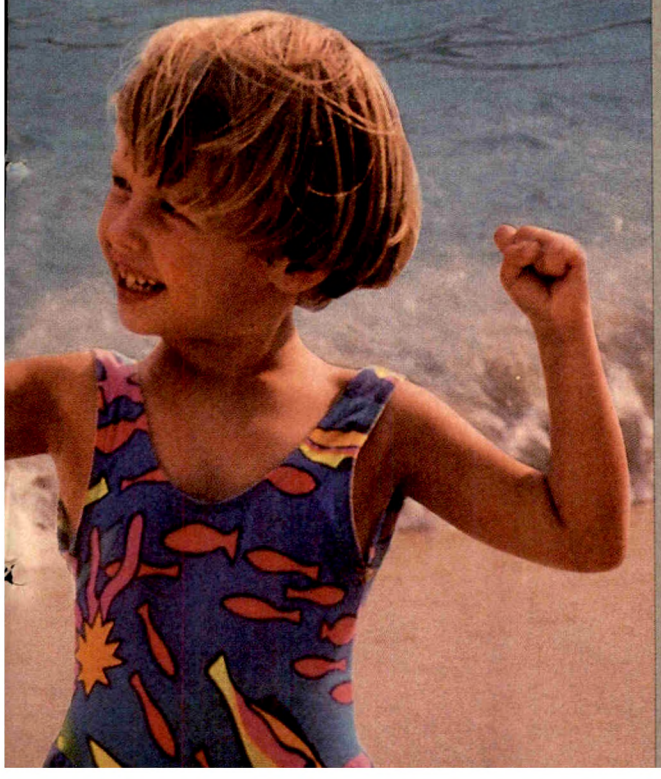
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Indications and Usage Ismo is indicated for prevention of angina pectoris due to coronary artery disease. The onset of action is not rapid enough for it to be useful in aborting an acute anginal episode.

Clinical Pharmacology Isosorbide mononitrate is the major active metabolite of isosorbide dinitrate; most of the clinical activity of the dinitrate comes from the mononitrate. Ismo is not subject to first-pass metabolism in the liver and the absolute bioavailability of isosorbide mononitrate from Ismo tablets is nearly 100%. The rate of clearance of Ismo is the same in healthy young adults, in patients with various degrees of renal, hepatic, or cardiac dysfunction, and in the elderly.

Several well-controlled studies have demonstrated that active nitrates were indistinguishable from placebo after 24 hours (or less) of continuous therapy due to the development of tolerance. Only after nitrates are absent from the body for several hours is their antianginal efficacy restored.

The drug-free interval sufficient to avoid tolerance to isosorbide mononitrate is not completely defined. The only regimen shown to avoid development of tolerance with isosorbide mononitrate involves two daily doses of Ismo tablets given 7 hours apart, so there is a gap of 17 hours between the second dose of each day and the first dose of the next day. Taking account of the relatively long half-life of isosorbide mononitrate this result is consistent with those obtained for other organic nitrates.

The same twice-daily regimen of Ismo tablets successfully avoided significant rebound/withdrawal effects. In studies of other nitrates, the incidence and magnitude of such phenomena appear to be highly dependent upon the schedule of nitrate administration.

Contraindications Allergic reactions are extremely rare, but do occur. Ismo is contraindicated in patients allergic to it.

Warnings Because the effects of Ismo are difficult to terminate rapidly and have not been established in patients with acute myocardial infarction (MI) or congestive heart failure (CHF), this drug is not recommended in these patients. If Ismo is used in these patients, careful clinical or hemodynamic monitoring is required to avoid the hazards of hypotension and tachycardia.

Precautions GENERAL Severe hypotension, particularly with upright posture, may occur with even small doses. Therefore, use with caution in patients who may be volume depleted or who are already hypotensive. Paradoxical bradycardia and increased angina pectoris may accompany Ismo-induced hypotension.

Nitrates may aggravate angina caused by hypertrophic cardiomyopathy.

INFORMATION FOR PATIENTS Tell patients they must carefully follow the prescribed dosing schedule (2 doses taken 7 hours apart) to maintain the antianginal effect (eg, take first dose on awakening and second dose 7 hours later).

Daily headaches sometimes accompany treatment with nitrates, including Ismo, and are a marker of drug activity. Patients with headaches should not alter their treatment schedule since loss of headache may be associated with simultaneous loss of antianginal efficacy. Headaches may be treated with aspirin and/or acetaminophen without affecting the antianginal activity of Ismo.

Light-headedness on standing, especially just after rising from a recumbent or seated position, may occur. This may be more frequent in patients who have consumed alcohol.

DRUG INTERACTIONS Vasodilating effects of Ismo may be additive with those of other vasodilators, especially alcohol.

Marked symptomatic orthostatic hypotension has been reported when calcium channel blockers and organic nitrates were used in combination. Dose adjustments of either class of agents may be necessary.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY No carcinogenic effects were observed in mice or rats exposed to oral Ismo, nor were adverse effects on rat fertility observed.

No mutagenic activity was seen in *in vitro* or *in vivo* assays.

PREGNANCY CATEGORY C Ismo has been shown to have embryocidal effects in rats and rabbits at doses at least 70 times the maximum human dose. There are no adequate and well-controlled studies in pregnant women. Use during pregnancy only if potential benefit justifies potential fetal risk.

NURSING MOTHERS Excretion in human milk is unknown. Use caution if administered to a nursing woman.

PEDIATRIC USE Safety and effectiveness have not been established.

Adverse Reactions Frequency of Adverse Reactions (Discontinuations)* Occurring in >1% of Subjects

	6 Controlled U.S. Studies		92 Clinical Studies
Dose	Placebo	20 mg	(varied)
Patients	204	219	3344
Headache	9% (0%)	38% (9%)	19% (4.3%)
Dizziness	1% (0%)	5% (1%)	3% (0.2%)
Nausea, Vomiting	<1% (0%)	4% (3%)	2% (0.2%)

*Some individuals discontinued for multiple reasons

Fewer than 1% of patients reported each of the following (in many cases a causal relationship is uncertain): *Cardiovascular;* angina pectoris, arrhythmias, atrial fibrillation, hypotension, palpitations, postural hypotension, premature ventricular contractions, supraventricular tachycardia, syncope. *Dermatologic;* pruritus, rash. *Gastrointestinal;* abdominal pain, diarrhea, dyspepsia, tenesmus, tooth disorder, vomiting. *Genitourinary;* dysuria, impotence, urinary frequency. *Miscellaneous;* asthenia, blurred vision, cold sweat, diplopia, edema, malaise, neck stiffness, rigors. *Musculoskeletal;* arthralgia. *Neurologic;* agitation, anxiety, confusion, dyscoordination, hypoesthesia, hypokinesia, increased appetite, insomnia, nervousness, nightmares. *Respiratory;* bronchitis, pneumonia, upper respiratory tract infection.

Rarely, ordinary doses of organic nitrates have caused methemoglobinemia in normal-seeming patients (See **Overdosage**).

Overdosage The ill effects of overdosage are generally related to the ability of Ismo to induce vasodilation, venous pooling, reduced cardiac output and hypotension. Symptoms may include increased intracranial pressure, with any or all of persistent throbbing headache, confusion, and moderate fever; vertigo; palpitations; visual disturbances; nausea and vomiting (possibly with colic and even bloody diarrhea); syncope (especially with upright posture); air hunger and dyspnea, later followed by reduced ventilatory effort; diaphoresis, with the skin either flushed or cold and clammy; heart block and bradycardia; paralysis; coma; seizures and death.

Serum levels have no role in managing overdose. The likely lethal dose in humans is unknown.

There is neither a specific antidote to Ismo overdose, nor data to suggest a means for accelerating its elimination from the body; dialysis is ineffective. Hypotension associated with Ismo overdose results from venodilatation and arterial hypovolemia; therefore, direct therapy toward an increase in central fluid volume. Use of arterial vasoconstrictors (eg, epinephrine) is likely to do more harm than good. In patients with renal disease or CHF, treatment of Ismo overdose may be difficult and require invasive monitoring.

Methemoglobinemia has occurred in patients receiving other organic nitrates, and probably could occur as a side effect of Ismo. There are case reports of significant methemoglobinemia in association with moderate overdoses of organic nitrates. None of the affected patients had been thought to be unusually susceptible. Suspect the diagnosis in patients who exhibit signs of impaired oxygen delivery despite adequate cardiac output and adequate arterial pO_2. Classically, methemoglobinemic blood is chocolate brown, without color change on exposure to air. The treatment of choice for methemoglobinemia is methylene blue, 1-2 mg/kg intravenously.

DOSAGE AND ADMINISTRATION The recommended regimen of Ismo tablets is 20 mg (one tablet) twice daily, with the two doses given 7 hours apart. For most patients, this can be accomplished by taking the first dose on awakening and the second dose 7 hours later. This dosing regimen provides a daily nitrate-free interval to avoid the development of refractory tolerance (see **Clinical Pharmacology**).

Well-controlled studies have shown that tolerance to Ismo tablets is avoided when using the twice daily regimen in which the two doses are given 7 hours apart. This regimen has been shown to have antianginal efficacy beginning 1 hour after the first dose and lasting at least 5 hours after the second dose. The duration (if any) of antianginal activity beyond 12 hours has not been studied; large controlled studies with other nitrates suggest that no dosing regimen should be expected to provide more than 12 hours of continuous antianginal efficacy per day.

Dosage adjustments are not necessary in the elderly patients or in patients with altered renal or hepatic function.

This Brief Summary is based upon the current Ismo direction circular, CI 4127-1, Issued January 10, 1992.

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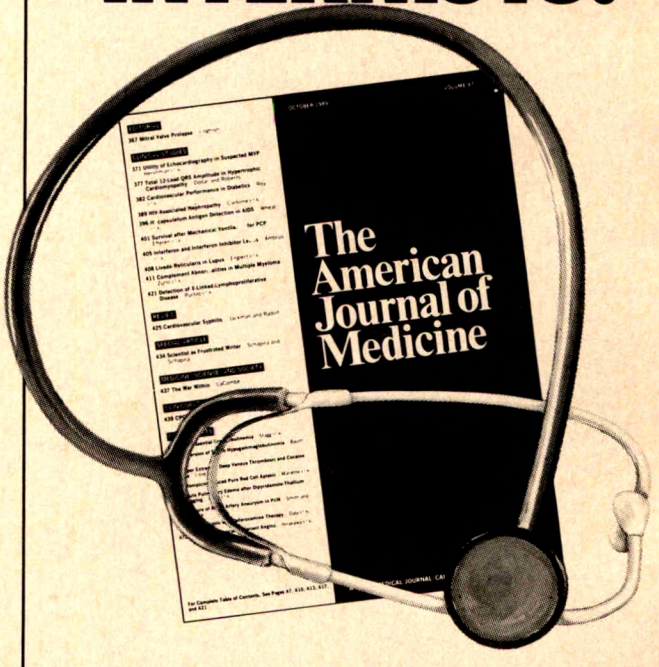
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Dimensions of the Triangle of Koch in Humans

Mark A. McGuire, FRACP, David C. Johnson, FRACS, Monica Robotin, MB, BS, David A. Richards, FRACP, John B. Uther, FRACP, and David L. Ross, FRACP

The atrioventricular (AV) node is situated in the lower atrial septum at the apex of a triangle described by Koch.[1] The sides of Koch's triangle are formed by the tendon of Todaro and the tricuspid annulus. The base is marked by the coronary sinus orifice (Figure 1). At the apex of the triangle the AV node penetrates the central fibrous body to become the His bundle. Increasing interest is now focused on this region because several techniques have been developed for the cure of supraventricular arrhythmias arising near the AV node.[2–4] Both surgical and catheter ablation techniques make use of the anatomic landmarks of Koch's triangle.[2–4] The aim of the current study was to define the size and variability of Koch's triangle in the human.

The dimensions of Koch's triangle were determined in 65 human adult hearts. The distance from the central fibrous body to the nearest edge of the coronary sinus (henceforth referred to as the length of Koch's triangle) and the distance from the tricuspid annulus to the nearest edge of the coronary sinus (henceforth referred to as the height of Koch's triangle) were measured using calipers (see Figure 1). In 20 cases (31%) these measurements were obtained at postmortem examination; the remaining dimensions were measured under direct vision during surgical procedures for the cure of supraventricular tachycardia (either AV junctional reentrant tachycardia, right atrial tachycardia or tachycardia associated with accessory AV pathways in the posterior septal space or right free wall of the heart). Most patients undergoing arrhythmia surgery had normal hearts but 6 had coronary artery disease and 2 had atrial septal defects. Abnormalities of the AV junctional area were not present in any of the hearts studied at postmortem examination. Evidence of significant coronary artery disease was present in 7 of the postmortem hearts and left ventricular hypertrophy was present in 3. The mean age of the patients was 46 ± 19 years and 41 (63%) were women. The preponderance of women reflected the higher proportion of women undergoing arrhythmia surgery. The relations between heart weight and the dimensions of Koch's triangle were determined in the hearts studied at postmortem examination. The relations between height, body weight, body surface area and dimensions of Koch's triangle were determined in all hearts. These relations were determined using simple linear regression. Comparisons of group means were performed using the unpaired t test. Values are expressed as mean ± standard deviation unless otherwise stated.

The mean length of Koch's triangle was 17 ± 3 mm (range 10 to 24). In 90% of cases the length of the triangle was between 14 and 20 mm. The mean height of Koch's triangle was 13 ± 3 mm (range 6 to 21). In 90% of cases the height was between 10 and 17 mm. The mean length of the triangle measured in postmortem hearts was similar to that measured at arrhythmia surgery (length 17 ± 2 vs 17 ± 3 mm, p = not significant [NS]). The mean height of the triangle measured in postmortem hearts was slightly greater than that measured at arrhythmia surgery (15 ± 4 vs 13 ± 3 mm, p <0.05), possibly as a result of atrial enlargement in some of the

From the Cardiology Unit, Westmead Hospital, Sydney, New South Wales 2145, Australia. This work was supported in part by a grant-in-aid from the National Heart Foundation of Australia, ACT, 2606, Australia. Dr. McGuire is a recipient of a Postgraduate Medical Research Scholarship from the National Health and Medical Research Council of Australia, ACT, 2606, Australia. Manuscript received February 18, 1992; revised manuscript received May 7, 1992, and accepted May 10.

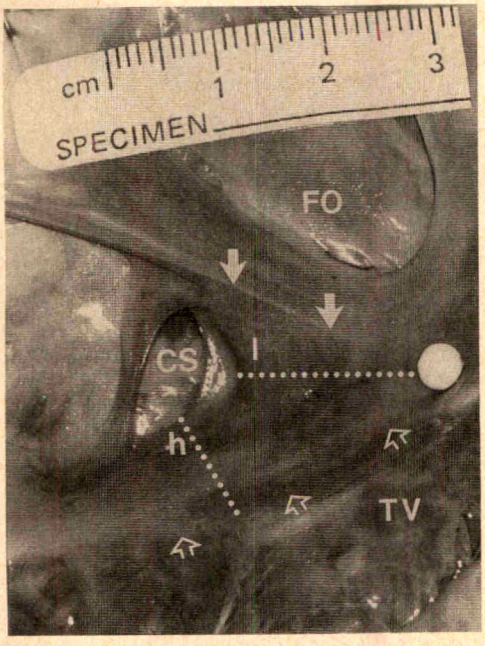


FIGURE 1. The triangle of Koch is found just above the septal leaflet of the tricuspid valve (TV). It is bounded by the tendon of Todaro *(solid arrows)* and the tricuspid annulus *(open arrows)*. The mean distance from the nearest edge of the coronary sinus orifice (CS) to the central fibrous body *(marked by white pin)* was 17 ± 3 mm *(dashed line marked* l) and the mean distance from nearest edge of the coronary sinus orifice to the tricuspid annulus was 13 ± 3 mm *(dashed line marked* h). FO = fossa ovalis.

TABLE I Relation Between Dimensions of Koch's Triangle and Patient Characteristics

Variables	r^2	p Value
Length of Koch's triangle and body weight	0.004	NS
Length of Koch's triangle and body height	0.012	NS
Length of Koch's triangle and body surface area	0.001	NS
Length of Koch's triangle and heart weight	0.239	<0.05
Height of Koch's triangle and body weight	0.012	NS
Height of Koch's triangle and body height	0.004	NS
Height of Koch's triangle and body surface area	0.005	NS
Height of Koch's triangle and heart weight	0.005	NS

NS = not significant.

postmortem hearts. The dimensions found in men were not different from those found in women (length 18 ± 3 vs 17 ± 3 mm, p = NS; height 14 ± 3 vs 13 ± 3 mm, p = NS) despite men being taller (174 ± 9 vs 163 ± 7 cm, p <0.001), heavier (72 ± 18 vs 62 ± 15 kg, p <0.05) and having larger body surface areas (1.8 ± 0.2 vs 1.6 ± 0.2 m^2, p <0.01). Both the length and height of Koch's triangle correlated poorly with height, body weight and body surface area (Table I). The length of the triangle but not its height correlated with heart weight (Table I).

These data indicate that Koch's triangle is of relatively uniform size and is not markedly affected by body size or gender in adult patients. The length of the triangle correlated with heart weight but the variation in size was not great. This information may prove useful in treating posterior septal accessory pathways and AV junctional reentrant tachycardia. The anatomic boundaries of Koch's Triangle are used as landmarks when attempting catheter ablation of these arrhythmias.[4] For example, previously published work indicates that the AV node is <7 mm long[5] and that the lesions produced by radiofrequency energy delivered through a catheter electrode are approximately 5 mm in length, breadth and height.[6] Thus radiofrequency lesions placed near the coronary sinus orifice in an attempt to ablate posterior septal accessory pathways are unlikely to damage the AV node directly, even in patients of small stature. These findings are consistent with the low incidence of unintentional complete heart block observed during radiofrequency ablation therapy of this arrhythmia. These data may also be useful in the design of plaque electrodes for use in mapping electrical activation in the region surrounding the AV node.

Acknowledgment: We would like to thank Graham Nunn, MD, William Meldrum-Hanna, MD, and Diane Little, MD, for providing cases for this study.

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Does Delayed Loss of Preexcitation After Unsuccessful Radiofrequency Catheter Ablation of Accessory Pathways Result in Permanent Cure?

James W. Leitch, MB BS, George J. Klein, MD, Raymond Yee, MD, Richard A. Leather, MD, and You Ho Kim, MD

Unsuccessful radiofrequency catheter ablation of accessory atrioventricular (AV) pathways may be followed by subsequent spontaneous loss of preexcitation with apparent "delayed cure." The mechanism of this phenomenon is uncertain but may result from inflammation at the ablation site, adjacent to the accessory pathway. The aim of this study was to determine if delayed loss of accessory pathway conduction after unsuccessful catheter ablation resulted in permanent loss of accessory pathway conduction.

In our initial experience of radiofrequency catheter ablation of accessory pathways[1] there were 5 patients with delayed loss of accessory pathway conduction after unsuccessful ablation. In 1 patient, with a concealed accessory pathway, absent accessory pathway conduction was found at the time of epicardial surgery, 5 days after unsuccessful ablation. A wide left parietal epicardial dissection was performed based on the findings at the ablation study and accessory pathway conduction has not returned. This patient was excluded from the present study and the remaining 4 patients formed the study group.

Radiofrequency ablation was performed as previously described,[1–3] using a 7Fr deflectable catheter with a 4 mm long distal electrode (Mansfield-Webster, Watertown, Massachusetts). The energy source was either an electrosurgery unit (Valley Lab, Boulder, Colorado) delivering a 500 kHz continuous wave using coagulation energy monitored by an ammeter or a Radionics RFG-3C radiofrequency lesion generator (Radionics Inc., Burlington, Massachusetts). Radiofrequency energy was delivered at a current of 0.4 to 0.6 A and at a power output of 25 to 35 J. Current delivery was discontinued if accessory pathway conduction was still present after 5 to 10 seconds of ablation. Otherwise, current was applied for 60 seconds or until an impedance increase prevented further ablation.

Follow-up electrophysiologic studies were performed 2 to 5 days and again 3 to 5 months after ablation. Three quadripolar catheters were positioned in the high right atrium, right ventricular apex and His bundle recording position, and an octapolar catheter was positioned in the coronary sinus. Because accessory pathway effective refractory period determinations were sometimes obtained from different pacing sites before and after ablation, accessory pathway block cycle lengths were used for comparison.[4] If accessory pathway conduction was pres-

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ent but tachycardia not inducible, isoproterenol was infused at 1 to 2 μg/min and atrial and ventricular stimulation repeated.

Patient characteristics and electrophysiologic measurements are listed in Table I. All patients had a single accessory pathway with bidirectional conduction. A total of 17 ± 9 applications of radiofrequency energy were applied. Temporary loss of preexcitation occurred within 1 to 5 seconds of an application of radiofrequency current in the 3 patients with manifest preexcitation at

TABLE I Patient Characteristics and Electrophysiologic Measurements

			Before Ablation					End of Ablation			Early Follow-Up EP Study			Late Follow-Up EP Study			
Pt. No.	Age (yr)	Location	A BCL	R BCL	RT	Delta-V	Time to Loss	A BCL	R BCL	RT	A BCL	R BCL	RT	A BCL	R BCL	RT	Symptoms
1	18	Posteroseptal	250	260	+	0	4	Absent	Absent	—	Absent	Absent	—	300	250	+	+
2	34	Right lateral	360	340	+	−40	1	360	320	—	*	330	+	300	340	+ (Isuprel®)	—
3	17	Left lateral	800	280	+	NA	NA	Absent	540	—	Absent	Absent	—	250	280	+	+
4	23	Left lateral	360	700	—	−30	5	380	Absent	—	Absent	Absent	—	440	Absent	—	—
Mean	23		443	395		−23	3.33	370	430					323	290		
SD	8		244	206		21	2.08	14	156					82	46		

*Intermittent preexcitation.
A BCL = anterograde accessory pathway block cycle length; EP = electrophysiologic study; NA = not available; R BCL = retrograde accessory pathway block cycle length; RT = inducible reciprocating tachycardia; Time to loss = time from onset of ablation to loss of preexcitation; V = ventricular electrogram; — = absent; + = present.

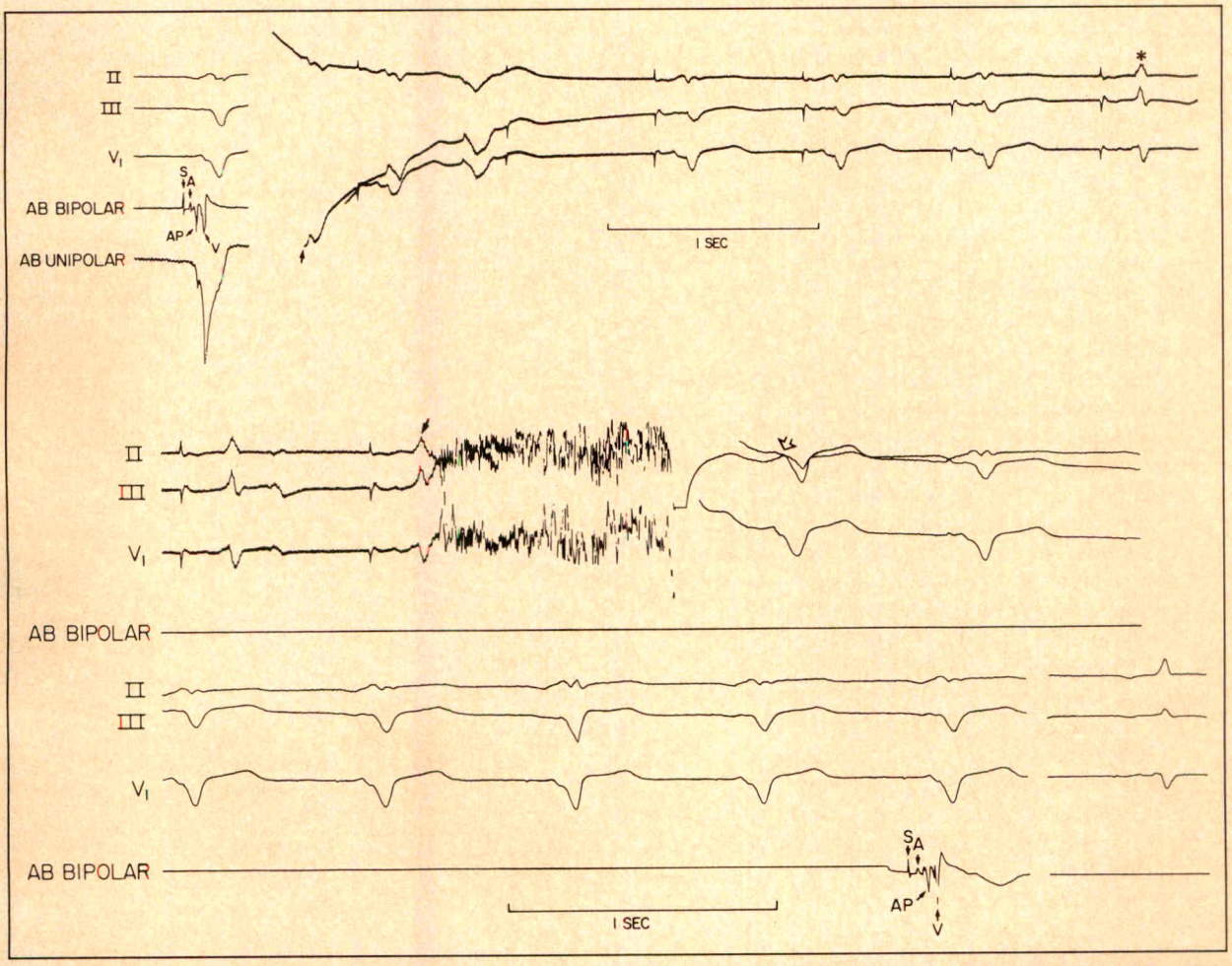


FIGURE 1. Ablation of a posteroseptal accessory pathway in patient 1. *Top,* the ablation catheter (AB), positioned at the orifice of the coronary sinus, recorded a possible accessory pathway potential (AP) on the bipolar recording and a sharp negative deflection on the unipolar recording from the distal electrode. However, preexcitation was not abolished until 4 seconds of ablation (* indicates loss of preexcitation). *Bottom,* after 12 seconds of ablation an increase in impedance occurred *(dark arrow, upper panel)* requiring immediate cessation of ablation. When current was discontinued, preexcitation returned *(light arrow).* The ablation electrogram was unchanged. After 5 minutes, without further ablation or catheter manipulation, preexcitation disappeared (shown in last complex of Figure 2). There was no recording from the ablation catheter at this time because it had been removed to clean off the coagulum. There was still no accessory pathway conduction at early follow-up study performed 2 days later, but accessory pathway conduction with inducible reciprocating tachycardia was present at late follow-up study. Bipolar filter settings were 5 to 250 Hz and unipolar filter settings 0.05 to 400. A = atrium; S = stimulus artefact; V = ventricle.

the time of ablation. Current was applied for a mean of 23 ± 11 seconds during the applications, which resulted in loss of accessory pathway conduction (range 12 to 34 seconds). The ventricular activation time at the initially successful ablation site, relative to the onset of the delta wave, ranged from 0 to −40 ms (mean of −23 ± 20). One patient (no. 1) lost all accessory pathway conduction 5 minutes after an unsuccessful application of radiofrequency energy, without further ablation or catheter manipulation (Figure 1). Accessory pathway conduction was still absent 2 days later at repeat electrophysiologic study. In 2 patients (nos. 2 and 4), preexcitation was present at the end of the ablation procedure but disappeared within 3 to 5 days of ablation. Repeat electrophysiologic study, performed within 24 hours of loss of preexcitation, disclosed no accessory pathway conduction in 1 patient and intermittent preexcitation with intact retrograde accessory pathway conduction in the other. The remaining patient (no. 3) continued to have retrograde accessory pathway conduction at the end of the ablation procedure but had no accessory pathway conduction at repeat study performed 5 days later.

Late follow up electrophysiologic study was performed 3.4 ± 2 months (range 3 to 5) after ablation. Accessory pathway conduction was present in all patients and tachycardia was inducible in 3 (the one patient without inducible tachycardia did not have inducible tachycardia at the preablation study). Anterograde and retrograde accessory pathway block cycle lengths were not significantly different from accessory pathway block cycle lengths before ablation (Table I). The accessory pathway delta wave polarity and location were unchanged in each patient.

Delayed loss of preexcitation after unsuccessful catheter ablation suggests that the injury induced by radiofrequency current may progress and obviate the need for repeat ablation or surgery in some patients. Unfortunately, this beneficial effect was only transient and normal accessory pathway conduction resumed within 5 months in the study patients. Similar progressive effects have been noted after radiofrequency catheter modification of AV node reentry with development of complete AV block 3 to 6 days after ablation.[5,6] Delayed onset of AV block has also been observed after direct-current ablation of a posteroseptal accessory pathway.[7] Whether heart block was permanent in these patients is uncertain. The experience of this study is also consistent with operative studies in which electrophysiologic studies performed in the first week after surgery did not detect a substantial number of subsequent recurrences.[8,9]

One possible explanation for delayed loss of accessory pathway conduction is edema and inflammation at the site of ablation, adjacent to the accessory pathway. Radiofrequency lesions induced in dogs are described as well demarcated areas with central necrosis when examined 1 week after ablation.[10–12] A rim of granulation tissue with histologic evidence of inflammatory cell infiltrate and hemorrhage surrounds the central zone of necrosis.[10] This inflammatory response may be sufficient to interrupt accessory pathway conduction temporarily without producing permanent destruction. The inflammatory response would be expected to be maximal in the first week, in keeping with loss of accessory pathway conduction 3 to 5 days after ablation in most patients. Two months after ablation, experimental radiofrequency lesions have healed, with the necrotic area replaced by granulation and scar tissue.[12] Absence of any significant effect in the study patients several months after ablation indicates that the accessory pathways were outside the area of necrosis induced by ablation.

The patients in this series were studied during our initial experience with catheter ablation. As operator experience increases[2,3] and with technical improvements in catheters and energy sources, unsuccessful ablation of accessory pathways is likely to be an uncommon event. If ablation is unsuccessful, the results of this study suggest that mapping during repeat procedures may be rendered difficult by absent or tenuous accessory pathway conduction in the first weeks after ablation. This was a particular problem in 1 patient who underwent surgery 5 days after unsuccessful ablation. Fortunately, the findings of the preoperative study allowed successful surgery in this instance.[13]

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Coronary Spasm and Cardiac Arrest After Coronary Arteriography in Unsuspected Thyrotoxicosis

Daniel Carey, MD, John W. Hurst, Jr., MD, and Mark E. Silverman, MD

Coronary artery spasm causing myocardial ischemia has been reported in thyrotoxicosis.[1,2] Patients with thyrotoxicosis may present with myocardial ischemia, but not necessarily have signs or symptoms that would alert the clinician to the underlying endocrine problem.[3] Coronary arteriography in these patients is potentially risky because of the iodine load contained in intravascular contrast agents. Although coronary arteriography is associated with a variety of complications (with most related to vascular injury or embolic phenomenon),[4] coronary spasm resulting in ventricular fibrillation hours after coronary arteriography has not been reported.

A 57-year-old woman was transferred for cardiac catheterization, because of persistent hypotension, tachycardia, pulmonary congestion and chest pain after laproscopic cholecystectomy. She was admitted 10 days previously with right upper quadrant pain radiating to the right chest and shoulder. Evaluation of the patient revealed gall stones, which were removed laproscopically together with the gall bladder.

After surgery, she had hypotension, and after fluid replacement, she developed pulmonary congestion, hypoxia needing intubation, and persistent abdominal and chest discomfort. Electrocardiograms obtained during pain showed no acute ischemic changes. Central venous pressure was 15 mm Hg. A cardiac catheterization to evaluate her pain and hemodynamic compromise revealed normal systolic function, left ventricular end-diastolic pressure of 22 mm Hg, mild luminal irregularities in the proximal left anterior descending artery, and 40% narrowing of the distal right coronary artery. Iohexol was used in the standard fashion for angiographic contrast. Approximately 12 hours after catheterization, she developed abdominal and chest discomfort similar to that which she had both before and after surgery, accompanied by nausea and diaphoresis, and was found to have new anterior ST-segment elevation (Figure 1). She subsequently developed ventricular tachycardia and fibrillation needing intubation and repeated countershock. Figure 2 shows her baseline tracing in the same lead in the absence of chest pain. She was treated with intravenous β blockade and nitroglycerin, and received sublingual nifedipine several times over the next 48 hours for repeated episodes of chest pain accompanied by reversible anterior ST-segment elevation. No evidence for acute myocardial infarction was documented by enzymes or serial electrocardiography.

Thyroid function studies after cardiac arrest revealed a thyroxine level of 23.8 μg/100 ml (upper limit of normal 4.5 to 12.0) and no detectable thyroid-stimulating hormone. She was treated for Graves' disease and has been asymptomatic since achieving a euthyroid state.

Our patient did not demonstrate the usual physical findings of hyperthyroidism (no goiter, lid lag, exophthalmos or tremor).[4] Her deterioration after surgery was attributed to hemodynamic compromise secondary to her unsuspected hyperthyroid condition that was exacerbated by the stress of surgery. Furthermore, the consistent pattern of pain before and after surgery, the documentation of ST elevation with pain, and its cessation after treatment of hyperthyroidism suggest an ischemic etiology.

The timing of her cardiac arrest and subsequent ischemic episodes after cardiac catheterization implicates iodine loading (in the form of an organically iodinated intravascular contrast agent) as the stimulus for her prolonged coronary spasm and resultant severe ischemia. Although almost all iodine remains organically bound, some deiodination occurs,[5] and hyperthyroid crises have been precipitated after use of intravascular contrast agents.[6] Wei et al[7] reported a similar sequence of ST-segment elevation followed by ventricular fibrillation in thyrotoxicosis, although not temporally related to coronary arteriography. Because of the intrinsic iodine load, arteriography may represent a serious risk to

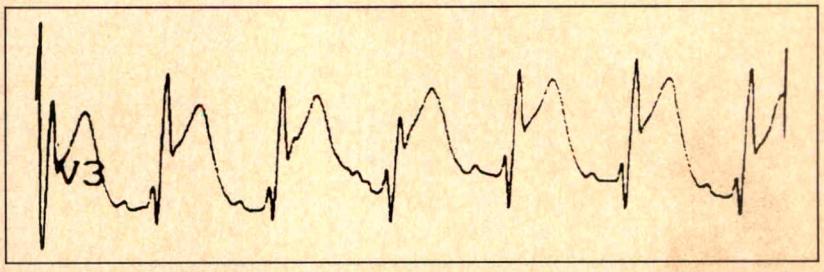


FIGURE 1. Lead V_3 of electrocardiogram during spontaneous chest pain showing ST-segment elevation.



FIGURE 2. Lead V_3 of baseline electrocardiogram after ischemic episode.

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patients with unsuspected hyperthyroidism by inducing or worsening coronary spasm.

Therefore, physicians considering coronary arteriography for the evaluation of patients with pain syndromes suggestive of coronary spasm need to have a high index of suspicion for possible concurrent thyroid disease. This procedure should be avoided in untreated thyrotoxicosis to prevent this rare but serious complication.

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Superficiality of Femoral Artery Pseudoaneurysm as a Risk Factor for Rupture

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Femoral artery pseudoaneurysm is a well-recognized complication of cardiac catheterization, percutaneous transluminal coronary angioplasty (PTCA) and other invasive vascular procedures.[1,2] Femoral artery pseudoaneurysms may be associated with many secondary complications including infection, distal embolization and, most often, hemorrhage. The reported risk factors for pseudoaneurysm hemorrhage or rupture are large size and anticoagulation. In this report we review 3 cases that suggest superficiality as an addition risk factor for pseudoaneurysm hemorrhage.

PATIENT 1: A 63-year-old man with unstable angina underwent PTCA of the acute marginal artery. A stent was placed across the lesion because of acute closure. He was treated with full-dose heparin for 5 days and coumadin therapy was initiated during the same period. On day 4 after PTCA, a small hematoma with associated systolic bruit was noted on physical exam. Duplex ultrasound showed a pseudoaneurysm (Figure 1) lying only 3 mm below the skin surface. Because of its small size, we elected to manage the pseudoaneurysm conservatively. On day 6 after PTCA the patient was discharged home taking aspirin, dipyridamole and coumadin. Within 24 hours, he returned to the emergency room with profuse bleeding from the right femoral area. Surgical exploration revealed active bleeding from a common femoral puncture site, which was oversewn. The patient made an uneventful recovery.

PATIENT 2: A 57-year-old man with angina underwent PTCA of the distal right coronary artery with stent placement. After the procedure he was given heparin and started on coumadin, dipyridamole and aspirin. On day 5 after PTCA, a large right groin ecchymosis with associated tenderness and bruit was noted. A duplex ultrasound showed a small (10 mm) aneurysm 7 mm below the skin. During the study, the patient began to have brisk, pulsatile bleeding from the puncture site. Compression was performed without successful hemostasis. Surgical exploration revealed a ruptured pseudoaneurysm originating from the common femoral artery. The patient did well postoperatively.

PATIENT 3: A 50-year-old man with progressive angina underwent PTCA of the left anterior descending artery. He received heparin for 36 hours after the procedure because of a coronary dissection. On day 2 after PTCA a small hematoma with a bruit was noted in the right groin. Duplex ultrasound showed a 14 × 15 mm pseudoaneurysm that was 8 mm below the skin surface. Because of the small size of the pseudoaneurysm, the patient was managed conservatively. He was discharged on day 2 after PTCA but presented again within 48 hours with a grape-

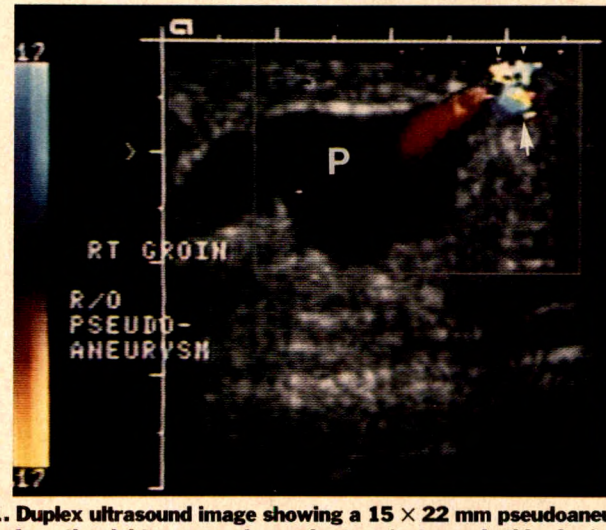


FIGURE 1. Duplex ultrasound image showing a 15 × 22 mm pseudoaneurysm (P) originating from the right common femoral artery (not seen in this view). Color flow Doppler reveals a *red jet* caused by systolic flow into the pseudoaneurysm. The neck of the pseudoaneurysm *(large arrow)* is superficial, with the most superficial portion *(small arrow)* being only 3 mm below the skin surface.

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fruit-sized groin mass and a continuous bruit over the area. Emergency surgery revealed a large hematoma and a bleeding branch of the common femoral artery, which was repaired. The patient's course was complicated by acute closure of the left anterior descending artery with a resultant infarct 1 day after operation. He was stabilized and discharged 1 week later.

From review of previous publications, and in common practice, small pseudoaneurysms (<2 cm diameter) have been thought to be at lower risk for rupture than their larger counterparts. Recently, many investigators have advocated nonsurgical management and observation for smaller pseudoaneurysms, especially those showing intraluminal clot.[3–5] However, in these cases, we have seen that significant hemorrhage and significant morbidity can result from very small pseudoaneurysms. The fact that 2 of 3 patients were receiving ongoing anticoagulation is notable since such therapy may have contributed to their tendency to bleed; however, none of the prothrombin times were greater than twice control at the time the hemorrhages occurred. All 3 patients had unusually superficial pseudoaneurysms: <1 cm below the skin surface. This suggests that superficiality may be an important risk factor for pseudoaneurysm rupture and hemorrhage.

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Simultaneous Mechanical Clot Fragmentation and Pharmacologic Thrombolysis in Acute Massive Pulmonary Embolism

We read with interest the report by Essop et al[1] of 5 patients severely compromised by acute massive pulmonary embolism who were successfully treated by mechanical fragmentation of the thrombus, followed by an infusion of streptokinase in the pulmonary artery. We recently reported a similar study of 3 such patients who presented with cardiogenic shock due to acute massive pulmonary embolism.[2] Fragmentation and distal dispersion of the occluding thrombus was performed using conventional diagnostic cardiac catheters. This caused a rapid and substantial increase in pulmonary blood flow and cardiac output, accompanied by considerable improvement in the patients' well-being. Preliminary data from a larger study of 28 cases showed important benefit in 21 of these patients, using similar techniques of clot fragmentation, followed by thrombolysis.[3]

The patients in these studies of acute massive pulmonary embolism develop circulatory collapse as a result of sudden obstruction to pulmonary blood flow and die very quickly. Previous emergency techniques were either surgical embolectomy (which has a high mortality and is not immediately available) or percutaneous catheter pulmonary embolectomy (a method of ensnaring and removing emboli).[4] The devices developed for these techniques are bulky, their insertion requires cut-down or use of a large sheath (with subsequent bleeding problems), and they have not been often used. Percutaneous catheter fragmentation was previously described,[5–9] but is not widely known. Essop et al,[1] Horstkotte et al[3] and ourselves have shown that standard cardiac catheters can be used safely to fragment and disperse obstructing thrombus. Because the volume of the thrombus is large compared with that of the main pulmonary arteries, but small when compared with the total volume of the smaller vessels, dispersion of the thrombus into the distal vessels will substantially increase pulmonary blood flow. Although Essop used the femoral approach in each case (as we did in 2 of 3 cases), the possible risk of dislodgement of further emboli may make an arm vein a wiser choice. Furthermore it remains uncertain whether thrombolysis after percutaneous clot fragmentation confers any additional benefit after the embolus has been dispersed.

This study of Essop et al[1] reinforces our belief that urgent percutaneous fragmentation and dispersal of the thrombus by use of standard cardiac catheters is important in the emergency management of patients with massive pulmonary embolism. This technique needs no more skill than does right heart catheterization and may have important benefits in this group of patients.

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4 March 1992

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Rapid Breakdown During Exposure to Daylight of Molsidomine When Administered by Continuous Intravenous Infusion

Molsidomine, an antianginosal drug, offers an alternative for the organic nitrates such as isosorbide dinitrate and nitroglycerin. The information leaflet included with molsidomine ampuls (Corvaton® intravenous 20 mg ampuls, Therabel Pharma, Brussels, Belgium) recommends protection of the solution and the perfusion set from light. In clinical practice these recommendations are not always strictly followed. In this study, simulated intravenous administration was performed using a 80 $\mu g \cdot ml^{-1}$ molsidomine dilution in saline in a 50 mL polyvinyl chloride infusion bag. As a reference, an unprotected infusion bag and an unprotected polyvinyl chloride infusion tubing (180 cm in length) were placed in a room illuminated with artificial daylight (fluorescence lamps, 125 Lux), completely shielded from sunlight (A). In the other setups the unprotected infusion bag and the unprotected infusion tubing were placed behind a window at sunny weather conditions ($\pm$ 2.8 10^5 Lux) (B). Under the same circumstances the molsidomine breakdown in an infusion bag, covered with aluminium foil, connected to an unprotected infusion tubing (C) and in an infusion bag, protected by a UV-cover (Avon Medicals Ltd., Redditch, United Kingdom), connected to an infusion tubing in which a UV filter was incorporated (Rehau AG & Co., Rehau, Germany) (D) were investigated. In all experiments the solution was dropped at a flow rate of 12.5 $ml \cdot h^{-1}$. During 3 hours, 1 ml

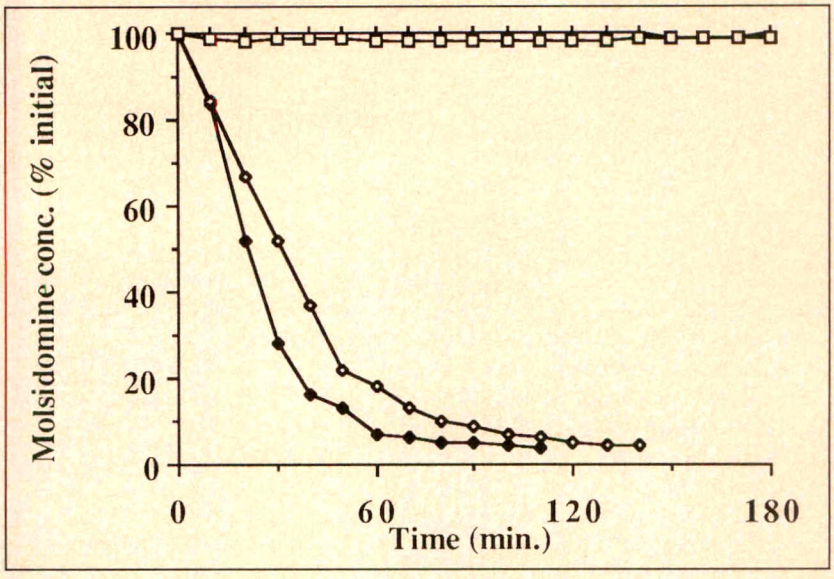


FIGURE 1. Molsidomine concentrations (conc.) (% initial) in function of time for setups A ( ), B ( ), C ( ) and D (□).

samples were taken at regular time intervals and analyzed by high-performance liquid chromatography.

The molsidomine samples from setup A showed no significant decrease in molsidomine concentration. This indicated that there was no sorption of the drug to the polymer material and that there was no stability problem when exposed to daylight. The samples taken at sunny weather conditions from setup B or C showed, after 1 hour exposure, a decrease in molsidomine concentration of about 90%. The decrease in molsidomine concentration after 1 hour exposure in setup D was only 2% (Figure 1).

The rapid breakdown of molsidomine in daylight observed in this experiment indicated that for the continuous intravenous administration (up to 48 hours) the recommendations on the leaflet need to be followed rigorously by using an appropriate UV cover for the infusion bag or syringe and UV filter for the tubing. This protection is not necessary when the solution is only exposed to artificial daylight.

Christian De Muynck
Geert M. R. Vandenbossche
Jean Paul Remon
Francis Colardyn
Gent, Belgium
18 March 1992

Left Ventricular Function in Myasthenia Gravis

I read with interest the report by Johannessen et al[1] on left ventricular (LV) function in myasthenia gravis. In the introduction, the authors state, "Previous studies of left ventricular (LV) systolic function have not reported abnormal cardiac findings." As a matter of fact, abnormalities of systolic function have been reported. Ashok et al[2] assessed LV function using systolic time interval and demonstrated abnormalities in 4 of 10 patients studied. More important, the abnormality reverted toward normal after injection of neostigmine.

Ahuja et al[3] used radionuclide scintigraphy to assess cardiac function. Although the baseline ejection fraction was within normal range in all 12 patients studied, 5 had significant improvement in ejection fraction after injection of neostigmine. Regional wall motion abnormality seen in 2 patients also reverted to normal after neostigmine. The authors speculated that circulating acetylcholine receptor antibodies may affect the acetylcholine receptors present in the heart muscle in a manner similar to skeletal muscles. Asthana et al[4] showed that antibodies from myasthenic patient's serum react equally well with receptors isolated from heart and skeletal muscles. Thus, there is evidence in the literature that LV function is affected in patients with myasthenia gravis.

G. K. Ahuja, FRCP
New Delhi, India
30 March 1992

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Beta Thromboglobulin and Increased Platelet Activation After Streptokinase Treatment of Acute Myocardial Infarction

In a recent issue of *The American Journal of Cardiology*, a careful and circumspect study was reported by Bertolino et al[1] concerning in vitro and ex vivo platelet functions during thrombolytic therapy of acute myocardial infarction (AMI). They gave a detailed analysis of the possible and debated actions of plasmin on platelet function, and pointed to the importance of platelet activation in the reocclusion of coronary blood vessels after the initially successful thrombolytic treatment of AMI, as well. Among other clinical studies, our modest results on increased platelet activation after streptokinase (SK) treatment of AMI were mentioned in their report.[2] They gave an account of the reduction of plasmatic β

Treatment of Acute Myocardial Infarction with Streptokinase		
	Reperfusion (n = 12)	No Reperfusion (n = 4)
B-TG (SD) (ng/ml)	256 (78)	187 (43)
TXB-2 (SD) (pg/ml)	269 (94)	117 (38)

B-TG = β thromboglobulin; TXB-2 = thromboxane-B-2.

thromboglobulin (B-TG) levels measured at the end of brief SK infusion and therefore did not find an explanation for our previous observations on increased B-TG levels after SK infusion.[2]

The interpretation and comparison of these 2 studies needs great caution. First, we did not measure B-TG concentrations before SK infusions and therefore could not make any conclusions on the early postinfusion changes of B-TG. The mean lag period between the onset of clinical signs and the initiation of thrombolytic therapy was >3 hours; thus, the difference between the timing of the 2 examinations may have a greater impact and more meaningful effect on the results, as was suggested by Bertolino.

Our later results suggest that our findings of increased platelet activation after SK treatment of AMI may at least in part be regarded as a consequence of a reperfusion/reoxygenation injury (see table).

The increase of the plasmatic level of von Willebrand factor antigen, together with the reduction of antithrombin-III antigen concentrations and protein C activity, was also more significant in the reperfusion group. (B-TG and the other parameters did not change considerably in a patient who received 5-day SK infusion therapy for inferior caval vein thrombosis.)

In many cases, platelet activation may be the consequence of reperfusion and reoxygenation itself after SK treatment of AMI (i.e., increased thromboxane metabolism,[2,3] thrombin-induced platelet activation,[4] and release of platelet-activating factor and other biologically active compounds[5]). The high incidence of thrombotic reocclusions after the initial success of thrombolytic therapy also seems to be consistent with our previously presented data.

Miklos Udvardy, MD
Jolan Harsfalvi, MD
Zoltan Boda, MD
Kalman Rak, MD
Debrecen, Hungary
2 April 1992

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Death in Opera: A Case Study, "Tales of Hoffman" — Antonia

The investigation of death on the operatic stage calls for the talents of a forensic pathologist. In the standard repertory, mayhem is rampant. An opera in point is "Tosca" by Giacomo Puccini. By curtain fall at the end of the third act, the 3 principals are dead: the baritone Scarpia murdered (a knife in his back) by Tosca, the tenor Cavaradossi shot by firing squad, and the soprano Tosca having leapt to her death from the parapet of the Castel Sant'Angelo. It is, for the audience, an extremely satisfying evening, because of the glorious music that accompanies these homicides/suicide.

But there are other works in which the cause of death onstage is less apparent. An opera in point is "Tales of Hoffman" by Jacques Offenbach, and in particular the third or "Antonia" act.

"Tales" was Offenbach's last opera and unfinished when he died in 1880 of complications of gout and heart disease. His librettists, Jules Barbier and Michel Carre, adapted their own stage play of 1851 for his musical setting; the stage play was based on 3 stories by the German author, musician and conductor, painter and designer, law student and Berlin Supreme Court councillor E. T. A. Hoffman, perhaps more famous for his fantastical story of the "Nutcracker and Mouseking." A prologue sets the tales: the narrator, Hoffman himself, awaits his current flame, a soprano, and to pass the time, he regales his fellow students with his stories. In each of the 3 acts that follows, Hoffman tells of an episode in his life in which he loses his beloved to a sinister figure, the devil in disguise. In the first act, he loses Olympia, a mechanical doll, to Coppelius, in the second, he loses a Venetian courtesan, Giulietta, to Dappertutto, and in the third, Antonia dies after the machinations of Dr. Miracle.

It is the third story (act) that requires forensic analysis. In 1819, Hoffman published "Rath Krespel" (Councillor Crespel),[1] in which a young woman sings to the tune of a violin made by her father, an elected official and amateur craftsman; as she reaches the topmost note of her song, his prized Cremonese violin shatters and she dies. The librettists made some changes for Offenbach's opera. In Robert Lawrence's analysis,[2] they "introduced the most effectively evil of characters, the slimy Dr. Miracle who, entering through the walls when the door is denied him, induces Antonia to sing herself to death while accompanying her on a macabre violin."

By what cause could singing induce the death of a young woman who has inherited from her mother, an opera singer who died under similar circumstances, a beautiful

voice and a frail physique? Offenbach helps the forensic pathologist here. It is near the end of the act, and Dr. Miracle appears magically to the consternation of Crespel and Hoffman who fear the doctor's evil ministrations. Dr. Miracle sings: "Nineteen. Glorious springtime of life. And now, let me take your pulse... Sh! Quiet while I count... Her pulse — very uneven and fast (inegal et vif). A dangerous symptom! Now sing! Now sing!" In the score, Offenbach has set the accompaniment in triplets (in duple rhythm, 3 sixteenth notes followed by a sixteenth note pause or rest) beginning with the taking of Antonia's pulse (stage direction) by Dr. Miracle. Antonia sings and dies, and another of Hoffman's loves is lost.

It should be noted that the use of musical values to represent the pulse goes back to Herophilus, a physician and contemporary of Aristotle in the fourth century BC, who interpreted the pulse according to "its rhythm or cadence which he likened to musical time and measures of verse."[3] In Nancy, France, in 1747 (with a second edition in 1769, in Amsterdam), Francois Nicolas Marquet published a book devoted to his special musical notation representing the varieties of palpated pulses.[4] "He stated that those accustomed to play on the lute made the best judges of the pulse!"[3]

Antonia has an inherited condition that under stress manifests itself as a cardiac arrhythmia followed by sudden death. Although the following discussion is speculative given the limited evidence, I believe, for the forensic pathologist, the differential diagnosis includes: (a) hereditary prolongation of the Q-T interval, (b) "malignant" hypertrophic cardiomyopathy, and (c) mitral valve prolapse.

Hereditary prolongation of the Q-T interval is a non-sex-linked autosomal dominant inherited condition in which the patient is prone to syncope, with ventricular fibrillation and sudden death. A few such families have been described,[5] some with associated neural deafness (the Romano-Ward syndrome, which is of recessive inheritance). But these are rare conditions, and many subjects affected have lived into the fifth decade.

"Malignant" hypertrophic cardiomyopathy has been characterized by sudden and unexpected death as the initial manifestation of cardiac disease,[6] often in the second or third decade of life. However, a third of these patients with sudden death have had chronic progressive heart failure or peripheral thromboembolic events. There are no defined patterns of inheritance.

Mitral valve prolapse was first described in the medical literature in 1963 when Barlow et al[7] reported on the clinical features associated with systolic clicks originating in the mitral apparatus. There is evidence to suggest that mitral valve prolapse is inherited as an autosomal dominant condition[8] and may also be associated with the inheritance, as an autosomal dominant, of a physical habitus characterized by narrow anterior posterior chest dimension and a longer arm span (a thin and frail appearance, perhaps a form fruste of the Marfan syndrome).[9]

Patients with the mitral valve prolapse syndrome may complain of shortness of breath and fatigue, and may be frail in spirit as well as in habitus. Cardiac arrhythmias and conduction abnormalities may be frequent, with both atrial and ventricular tachyarrhythmias well-described. Although the sudden death syndrome is rare, Chesler et al[10] reported 39 cases, predominantly women, in which 6 of 7 patients showed ventricular ectopy in electrocardiograms available before death. In their report, case 3 was a 14-year-old female who died suddenly and whose mother had died in similar circumstances at age 36. Kligfield et al[11] reviewed the literature and suggested that sudden death occurs more commonly in those patients with mitral valve prolapse who also have significant mitral regurgitation; these patients are also reported to have frequent and complex atrial and ventricular arrhythmias. The incidence may be as high as 0.5% annually, suggesting up to 4,000 deaths of which two thirds likely have hemodynamically significant mitral regurgitation and one third have no insufficiency. Whether increased plasma catecholamines related to stress ("Now sing! Now sing!") or present as an associated state of autonomic dysfunction/imbalance may predispose subjects to ventricular ectopy or catastrophic arrhythmia, or both, is not known, but has been suggested.[12]

Antonia sings and dies. An autopsy would show redundant mitral leaflets probably with annular dilatation, and myxomatous changes on microscopic examination. Antonia should have been treated with β-adrenergic blockers and could have then sung to her heart's content to a sedate and regular accompaniment, if to the loss of the dramatic and tragic, requisite to grand opera.

Leonard G. Dauber, MD
New York, New York
9 April 1991

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See also: Harding J. Jacques Offenbach, A Biography. New York: Riverrun Press, 1980; and Faris A. Jacques Offenbach. New York: Scribner's, 1980.

Water-Soluble Dietary Fiber and Low-Density Lipoprotein Cholesterol

Haskell et al (1) studied the effect of water-soluble dietary fiber of different sources on patients with hypercholesterolemia. To estimate low-density lipoprotein (LDL) cholesterol, they used the Friedewald formula.[2] This equation is based on the fact that the majority of circulating triglycerides (during fasting) are transported by very low density lipoprotein (VLDL). The amount of cholesterol bound to VLDL can be estimated because of a relatively constant proportion of cholesterol and triglycerides in VLDL. When triglycerides and cholesterol concentrations are expressed in mg/dL units, the Friedewald formula estimates VLDL cholesterol by dividing the concentration of triglycerides by 5. This is what Haskell et al claim to have done. Unfortunately, they did not use the mg/dL units, but rather the Système International (SI) units. As I have reported on a number of other occasions,[3–8] the divisor of the Friedewald equation becomes 2.18 instead of 5 with SI units, because the molecular weight of cholesterol is different from the average molecular weight of triglycerides. Although the majority of American investigators do their work in conventional units and convert the final results to SI units, this is rarely reported in their articles. This can lead the readers to think that the original equation is also valid with SI units. I previously reported 2 publications where the unadapted version of the equation was inappropriately applied.[9,10] Haskell et al made the same mistake. Although the reported concentrations of LDL cholesterol for their first study are correct (indicating that they only converted the final results in SI units), the concentrations reported for the 3 other studies are incorrect. They used the original version of the Friedewald formula after the other measurements were converted to SI units, resulting in an overestimation of LDL cholesterol (VLDL cholesterol being underestimated by using 5 instead of 2.18 as divisor). This error does not affect their final conclusions, since the variations of triglyceride concentrations were very similar between each group so that the overestimation was of the same order. I therefore reiterate my caution to investigators and readers that before using equations originally designed to be used with conventional units with SI units, one must check if a conversion factor is necessary. By the way, in Table III the change in triglycerides for their placebo group should read +0.025 (instead of +0.25) mmol/L or 1.66% (instead of 16.6%).

Jacques Massé, MD, MSc
Quebec City, Quebec, Canada
6 March 1992

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REPLY: Yes, unfortunately in the calculation for studies 2 to 4 reported in our manuscript, the factor used for converting triglycerides to VLDL cholesterol in SI units was 5.0 instead of 2.18. In study 1, the factor of 2.18 was correctly used. As pointed out by Massé, this error does not influence the results or conclusions of these studies. On average, this error results in the mean LDL cholesterol values we reported being approximately 9% higher in SI units than they actually were. For example, in study 3 (Table IV), the mean baseline values should have been 4.41 mmol/L instead of 4.76, and 3.88 mmol/L instead of 4.28 when the subjects were on the fiber mixture, with the decrease being −0.53 mmol/L instead of −0.54, and the percentage change being 12.0% instead of the reported 12.4.

William L. Haskell, PhD
Palo Alto, California
13 April 1992

Correction

In the article, "Transthoracic High-Frequency Two-Dimensional Echocardiography, Doppler and Color Flow Mapping to Determine Anatomy and Blood Flow Patterns in the Distal Left Anterior Descending Coronary Artery" by Antoinette Kenny and Leonard M. Shapiro, in the May 15, 1992 issue of the AJC, Figure 5A on page 1267 is mistakenly inverted.

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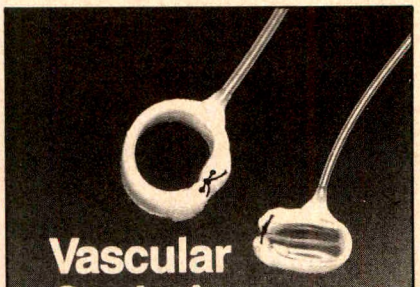
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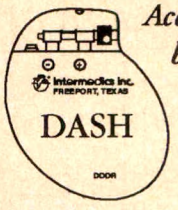
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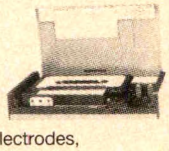
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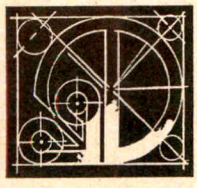
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Contact:
Charles Dennis, MD



Deborah Heart & Lung Center
200 Trenton Road
Browns Mills, NJ 08015
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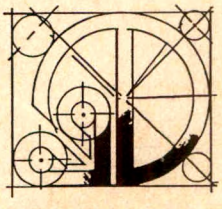
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Assistant/Associate Professor

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Or Call 800-344-7775

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Director, Pediatric Cardiology
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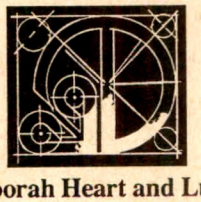
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CARDIZEM is contraindicated in (1) patients with sick sinus syndrome except in the presence of a functioning ventricular pacemaker, (2) patients with second- or third-degree AV block except in the presence of a functioning ventricular pacemaker, (3) patients with hypotension (less than 90 mm Hg systolic), (4) patients who have demonstrated hypersensitivity to the drug, and (5) patients with acute myocardial infarction and pulmonary congestion documented by X-ray on admission.

WARNINGS

1. Cardiac Conduction. CARDIZEM prolongs AV node refractory periods without significantly prolonging sinus node recovery time, except in patients with sick sinus syndrome. This effect may rarely result in abnormally slow heart rates (particularly in patients with sick sinus syndrome) or second- or third-degree AV block (13 of 3,007 patients or 0.43%). Concomitant use of diltiazem with beta-blockers or digitalis may result in additive effects on cardiac conduction. A patient with Prinzmetal's angina developed periods of asystole (2 to 5 seconds) after a single dose of 60 mg of diltiazem.

2. Congestive Heart Failure. Although diltiazem has a negative inotropic effect in isolated animal tissue preparations, hemodynamic studies in humans with normal ventricular function have not shown a reduction in cardiac index nor consistent negative effects on contractility (dp/dt). An acute study of oral diltiazem in patients with impaired ventricular function (ejection fraction 24% ± 6%) showed improvement in indices of ventricular function without significant decrease in contractile function (dp/dt). Worsening of congestive heart failure has been reported in patients with preexisting impairment of ventricular function. Experience with the use of CARDIZEM in combination with beta-blockers in patients with impaired ventricular function is limited. Caution should be exercised when using this combination.

3. Hypotension. Decreases in blood pressure associated with CARDIZEM therapy may occasionally result in symptomatic hypotension.

4. Acute Hepatic Injury. Mild elevations of transaminases with and without concomitant elevation in alkaline phosphatase and bilirubin have been observed in clinical studies. Such elevations were usually transient and frequently resolved even with continued diltiazem treatment. In rare instances, significant elevations in enzymes such as alkaline phosphatase, LDH, SGOT, SGPT, and other phenomena consistent with acute hepatic injury have been noted. These reactions tended to occur early after therapy initiation (1 to 8 weeks) and have been reversible upon discontinuation of drug therapy. The relationship to CARDIZEM is uncertain in some cases, but probable in some. (See PRECAUTIONS.)

PRECAUTIONS

General. CARDIZEM is extensively metabolized by the liver and excreted by the kidneys and in bile. As with any drug given over prolonged periods, laboratory parameters should be monitored at regular intervals. The drug should be used with caution in patients with impaired renal or hepatic function. In subacute and chronic dog and rat studies designed to produce toxicity, high doses of diltiazem were associated with hepatic damage. In special subacute hepatic studies, oral doses of 125 mg/kg and higher in rats were associated with histological changes in the liver which were reversible when the drug was discontinued. In dogs, doses of 20 mg/kg were also associated with hepatic changes; however, these changes were reversible with continued dosing.

Dermatological events (see ADVERSE REACTIONS section) may be transient and may disappear despite continued use of CARDIZEM. However, skin eruptions progressing to erythema multiforme and/or exfoliative dermatitis have also been infrequently reported. Should a dermatologic reaction persist, the drug should be discontinued.

Drug Interaction. Due to the potential for additive effects, caution and careful titration are warranted in patients receiving CARDIZEM concomitantly with any agents known to affect cardiac contractility and/or conduction. (See WARNINGS.) Pharmacologic studies indicate that there may be additive effects in prolonging AV conduction when using beta-blockers or digitalis concomitantly with CARDIZEM. (See WARNINGS.)

As with all drugs, care should be exercised when treating patients with multiple medications. CARDIZEM undergoes biotransformation by cytochrome P-450 mixed function oxidase. Coadministration of CARDIZEM with other agents which follow the same route of biotransformation may result in the competitive inhibition of metabolism. Dosages of similarly metabolized drugs such as cyclosporin, particularly those of low therapeutic ratio or in patients with renal and/or hepatic impairment, may require adjustment when starting or stopping concomitantly administered CARDIZEM to maintain optimum therapeutic blood levels.

Beta-blockers: Controlled and uncontrolled domestic studies suggest that concomitant use of CARDIZEM and beta-blockers is usually well tolerated, but available data are not sufficient to predict the effects of concomitant treatment in patients with left ventricular dysfunction or cardiac conduction abnormalities.

Administration of CARDIZEM (diltiazem hydrochloride) concomitantly with propranolol in five normal volunteers resulted in increased propranolol levels in all subjects and bioavailability of propranolol was increased approximately 50%. If combination therapy is initiated or withdrawn in conjunction with propranolol, an adjustment in the propranolol dose may be warranted. (See WARNINGS.)

Cimetidine: A study in six healthy volunteers has shown a significant increase in peak diltiazem plasma levels (58%) and area-under-the-curve (53%) after a 1-week course of cimetidine at 1,200 mg per day and diltiazem 60 mg per day. Ranitidine produced smaller, nonsignificant increases. The effect may be mediated by cimetidine's known inhibition of hepatic cytochrome P-450, the enzyme system probably responsible for the first-pass metabolism of diltiazem. Patients currently receiving diltiazem therapy should be carefully monitored for a change in pharmacological effect when initiating and discontinuing therapy with cimetidine. An adjustment in the diltiazem dose may be warranted.

Digitalis: Administration of CARDIZEM with digoxin in 24 healthy male subjects increased plasma digoxin concentrations approximately 20%. Another investigator found no increase in digoxin levels in 12 patients with coronary artery disease. Since there have been conflicting results regarding the effect of digoxin levels, it is recommended that digoxin levels be monitored when initiating, adjusting, and discontinuing CARDIZEM therapy to avoid possible over- or under-digitalization. (See WARNINGS.)

Anesthetics: The depression of cardiac contractility, conductivity, and automaticity as well as the vascular dilation associated with anesthetics may be potentiated by calcium channel blockers. When used concomitantly, anesthetics and calcium blockers should be titrated carefully.

Carcinogenesis, Mutagenesis, Impairment of Fertility. A 24-month study in rats at oral dosage levels of up to 100 mg/kg/day, and a 21-month study in mice at oral dosage levels of up to 30 mg/kg/day showed no evidence of carcinogenicity. There was also no mutagenic response in vitro or in vivo in mammalian cell assays or in vitro in bacteria. No evidence of impaired fertility was observed in a study performed in male and female rats at oral dosages of up to 100 mg/kg/day.

Pregnancy. Category C. Reproduction studies have been conducted in mice, rats, and rabbits. Administration of doses ranging from five to ten times greater (on a mg/kg basis) than the daily recommended therapeutic dose has resulted in embryo and fetal lethality. These doses, in some studies, have been reported to cause skeletal abnormalities. In the perinatal/postnatal studies, there was an increased incidence of stillbirths at doses of 20 times the human dose or greater.

There are no well-controlled studies in pregnant women; therefore, use CARDIZEM in pregnant women only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers. Diltiazem is excreted in human milk. One report suggests that concentrations in breast milk may approximate serum levels. If use of CARDIZEM is deemed essential, an alternative method of infant feeding should be instituted.

Pediatric Use. Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Serious adverse reactions have been rare in studies carried out to date, but it should be recognized that patients with impaired ventricular function and cardiac conduction abnormalities have usually been excluded from these studies.

The adverse events described below represent events observed in clinical studies of hypertensive patients receiving either CARDIZEM Tablets or CARDIZEM SR Capsules as well as experiences observed in studies of angina and during marketing. The most common events in hypertension studies are shown in a table with rates in placebo patients shown for comparison. Less common events are listed by body system; these include any adverse reactions seen in angina studies that were not observed in hypertension studies. In all hypertensive patients taking CARDIZEM Tablets or CARDIZEM SR Capsules studied (over 900), the most common adverse events were edema (9%), headache (8%), dizziness (6%), asthenia (5%), sinus bradycardia (3%), flushing (3%), and first-degree AV block (3%). Only edema and perhaps bradycardia and dizziness were dose related.

DOUBLE BLIND PLACEBO CONTROLLED HYPERTENSION TRIALS

ADVERSE	DILTIAZEM N=315 # PTS (%)	PLACEBO N=211 # PTS (%)
Headache	38 (12%)	17 (8%)
AV Block First Degree	24 (7.6%)	4 (1.9%)
Dizziness	22 (7%)	6 (2.8%)
Edema	19 (6%)	2 (0.9%)
Bradycardia	19 (6%)	3 (1.4%)
ECG Abnormality	13 (4.1%)	3 (1.4%)
Asthenia	10 (3.2%)	1 (0.5%)
Constipation	5 (1.6%)	2 (0.9%)
Dyspepsia	4 (1.3%)	1 (0.5%)
Nausea	4 (1.3%)	2 (0.9%)
Palpitations	4 (1.3%)	2 (0.9%)
Polyuria	4 (1.3%)	2 (0.9%)
Somnolence	4 (1.3%)	—
Alk Phos Increase	3 (1%)	1 (0.5%)
Hypotension	3 (1%)	1 (0.5%)
Insomnia	3 (1%)	1 (0.5%)
Rash	3 (1%)	1 (0.5%)
AV Block Second Degree	2 (0.6%)	—

The following table presents the most common adverse reactions reported in placebo-controlled trials in patients receiving CARDIZEM CD up to 360 mg with rates in placebo patients shown for comparison.

ADVERSE REACTION	CARDIZEM CD N=324	PLACEBO N=175
HEADACHE	9.0%	8.0%
BRADYCARDIA	4.3%	2.3%
EDEMA	3.7%	2.3%
DIZZINESS	3.1%	3.4%
ECG ABNORMALITY	3.1%	2.9%
AV BLOCK FIRST DEGREE	2.2%	—
ASTHENIA	1.9%	1.7%

In clinical trials of CARDIZEM CD Capsules, CARDIZEM Tablets, and CARDIZEM SR Capsules involving over 3000 patients, the most common events (ie, greater than 1%) were edema (4.9%), headache (4.9%), dizziness (3.5%), asthenia (2.7%), first-degree AV block (2.2%), bradycardia (1.6%), flushing (1.5%), nausea (1.4%), rash (1.3%), and dyspepsia (1.2%).

In addition, the following events were reported infrequently (less than 1%).

Cardiovascular: Angina, arrhythmia, AV block (second- or third-degree), bundle branch block, congestive heart failure, ECG abnormalities, hypotension, palpitations, syncope, tachycardia, ventricular extrasystoles.

Nervous System: Abnormal dreams, amnesia, depression, gait abnormality, hallucinations, insomnia, nervousness, paresthesia, personality change, somnolence, tinnitus, tremor.

Gastrointestinal: Anorexia, constipation, diarrhea, dry mouth, dysgeusia, mild elevations of SGOT, SGPT, LDH, and alkaline phosphatase (see hepatic warnings), thirst, vomiting, weight increase.

Dermatological: Petechiae, photosensitivity, pruritus, urticaria.

Other: Amblyopia, CPK increase, dyspnea, epistaxis, eye irritation, hyperglycemia, hyperuricemia, impotence, muscle cramps, nasal congestion, nocturia, osteoarticular pain, polyuria, sexual difficulties.

The following postmarketing events have been reported infrequently in patients receiving CARDIZEM: alopecia, erythema multiforme, exfoliative dermatitis, extrapyramidal symptoms, gingival hyperplasia, hemolytic anemia, increased bleeding time, leukopenia, purpura, retinopathy, and thrombocytopenia. In addition, events such as myocardial infarction have been observed which are not readily distinguishable from the natural history of the disease in these patients. A number of well-documented cases of generalized rash, characterized as leukocytoclastic vasculitis, have been reported. However, a definitive cause and effect relationship between these events and CARDIZEM therapy is yet to be established.

HOW SUPPLIED

CARDIZEM® CD (diltiazem hydrochloride) is available as capsules of 180 mg, 240 mg, and 300 mg in bottles of 30 and 90, and in UDIP® packages of 100.

CARDIZEM® SR (diltiazem hydrochloride) is available as sustained release capsules of 60 mg, 90 mg, and 120 mg in bottles of 100, and in UDIP® packages of 100.

CARDIZEM® CD Product Information as of October 1991

CARDIZEM® SR Product Information as of January 1991

References: **1.** Data on file, Marion Merrell Dow Inc. **2.** Cramer JA, Mattson RH, Prevey ML, et al. *JAMA.* 1989;261(22):3273-3274.

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The American Journal of Cardiology®

DECEMBER 21, 1992

A Symposium: Cardioprotection: Building a Consensus for the 1990s

GUEST EDITOR:

William H. Frishman, MD
Professor of Medicine and Epidemiology
Associate Chairman, Department of Medicine
Albert Einstein College of Medicine
Montefiore Medical Center
Bronx, New York

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This symposium was held on November 10, 1991, in Yorba Linda, California, and was sponsored by Albert Einstein College of Medicine and Montefiore Medical Center under an educational grant from Astra Pharmaceutical Products, Inc., Westborough, Massachusetts.

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THE AMERICAN JOURNAL OF CARDIOLOGY.® (ISSN 0002-9149) (GST 123397457) December 21, 1992, Vol. 70, No. 21 (USPS: 505–750).

Member, American Business Press, Inc. and Audit Bureau of Circulations. Published 5 times in April and November, 4 times in June and December, 3 times in January, March, May, August, September, and October, and 2 times in February, and July, by The Cahners Publishing Company, a Division of Reed Publishing USA, 275 Washington St., Newton, MA 02158-1630. Terrence M. McDermott, President and Chief Operating Officer; Frank Sibley, Executive Vice-President; Robert T. Brawn, Senior Vice President/General Manager; Jerry D. Neth, Senior Vice President/Publishing Operations; J.J. Walsh, Senior Vice President/Finance; Thomas J. Dellamaria, Senior Vice President/Production and Manufacturing; Ralph Knupp, Vice President/Human Resources. Printed in Easton, Pennsylvania.

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Subscription rate for individuals in field of publication: United States 1 year $66, 2 years $112, 3 years $158; Canada and Mexico 1 year $105, 2 years $178, 3 years $252. All other countries (prices include air-speeded delivery) 1 year $175, 2 years $306, 3 years $437. US institutions 1 year $95, 2 years $162, 3 years $228; Canada and Mexico 1 year $120, 2 years $200, 3 years $295; All other countries (prices include air-speeded delivery) 1 year $200, 2 years $350, 3 years $500. Special rate to U.S. Residents, Interns, Medical Students $33. The Journal is not responsible for replacing missing issues unless the Circulation Department is notified of nonreceipt within 3 months of issue date.

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MANUSCRIPTS: Address all manuscripts to William C. Roberts, MD, Editor in Chief, The American Journal of Cardiology, 7960 Old Georgetown Road, Suite 2C, Bethesda, Maryland 20814.

POSTMASTER: Send address changes to: The American Journal of Cardiology, P.O. Box 173377, Denver, Colorado 80217-3377.

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Editor's suggestion: The symposium issues for a full year should be bound together separately from the regular issues.

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The American Journal of Cardiology®

Introduction

William H. Frishman, MD

Over the years, various pharmacologic and nonpharmacologic interventions have been employed to protect the heart from structural damage or provide "cardioprotection." The goals of cardioprotection are to preserve the character and integrity of the coronary arteries and the myocardium. By reducing elevated blood pressure and elevated low-density lipoprotein (LDL)-cholesterol levels in patients, damage to the vascular and myocardial structures can be reduced. Ultimately, the goals of cardioprotective therapy are to extend the periods during which the coronary blood vessels and the myocardium remain functional.

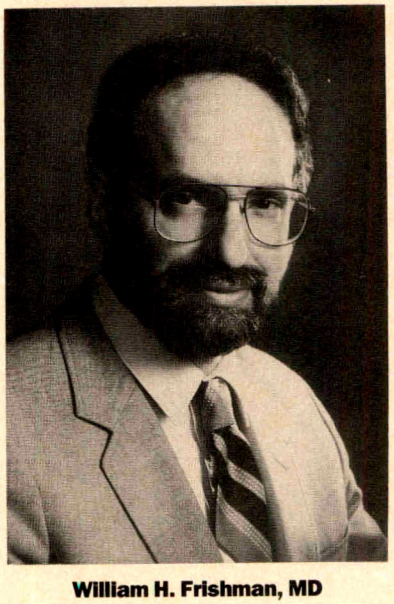
The concept of cardioprotection goes back many years. In the 1940s it was suggested that anticoagulation therapy might reduce the damage from coronary artery disease. Subsequently, other strategies were developed to protect the myocardium and the coronary arteries. These include the antiplatelet drugs, thrombolytic agents, angiotensin-converting enzyme (ACE) inhibitors, calcium antagonists, β-adrenergic blockers, and lipid-lowering drugs. Changes in patient life-style have also been explored. No single approach, however, has emerged as ideal. Cardioprotection appears to require a combination of interventions to achieve maximal benefit.

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The success of antihypertensive treatment in the United States is evident from the marked reductions reported in stroke morbidity and mortality. There is growing evidence that blood pressure- and lipid-lowering interventions can reduce the risks of coronary artery disease. Various pharmacologic therapies may prevent coronary thrombotic events and/or preserve myocardial functioning after myocardial infarction.

Cardioprotection is indeed an attainable goal. With judicious use of treatments discussed in this symposium, we will probably be witnessing even greater reductions in morbidity and mortality from cardiac and vascular diseases in the years to come.



William H. Frishman, MD

Beta-Adrenergic Blockers as Cardioprotective Agents

William H. Frishman, MD

The evidence supporting and describing cardioprotective effects of β-adrenergic blocker treatment is surveyed. Details of the many studies that individually and collectively document the ability of long-term and acute β-blocker therapy to reduce overall mortality, sudden cardiovascular death, and nonfatal reinfarction in patients surviving or experiencing a myocardial infarction are described. A discussion of the mechanisms by which β blockers probably and theoretically achieve these benefits includes the suggestion that they may reduce plaque rupture, thus indirectly inhibiting thrombosis. It is also suggested that, in the future, further cardioprotective benefits may accrue to the use of β blockers in conjunction with thrombolysis and of β blockers with a duration of action sustained throughout a full 24 hours.

(Am J Cardiol 1992;70:2 I–6 I)

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Beta-adrenergic blockers have proven to be safe and effective for the treatment of patients with various cardiovascular disorders.[1] These agents have always appeared as attractive preventive measures in patients because of their anti-ischemic, antiarrhythmic, and antihypertensive actions.[2] After the clinical introduction of propranolol for therapy of angina pectoris and arrhythmias, it was proposed that a β blocker might favorably influence the natural history of patients with myocardial infarction (MI) by attenuating the undesirable consequences of increased sympathetic nervous system activity.[3–5] Depression of left ventricular function, a major risk factor contributing to mortality after infarction, however, can be caused by β blockade.[1,3] For this reason, β blockers were initially avoided or used in small doses in patients with MI.

Since 1965, however, β blockers have been considered as possible therapies for extending life in patients surviving MI.[4] On the basis of multiple long-term clinical studies, the efficacy of these drugs in reducing the risk of mortality and nonfatal reinfarction in survivors of an acute MI has been demonstrated conclusively.[4,6] Beta blockers have also been shown to reduce the extent of myocardial injury and mortality during the acute phase of MI. Finally, they have been suggested for the primary prevention of MI and death in patients with hypertension and stable and unstable angina pectoris; their protective effects in these conditions, however, are less well-defined.[5]

LONG-TERM BETA-BLOCKER PREVENTION TRIALS

During the period from 1974 to 1990, 15 major randomized, controlled trials with β blockers have been reported, with treatment and mean follow-up extending from 9 months to 6 years.[7–27] More than 18,000 patients were studied and 10 different β blockers were evaluated in an attempt to document reductions in total mortality, cardiovascular mortality, sudden death, and nonfatal reinfarction. The 15 trials met the following criteria for study design:

TABLE I Results of Long-term (>9 Months) Beta-Blocker Trials

Trial	No. Patients (Randomized)		Mortality		
	Control	Intervention	Control (%)	Intervention (%)	p Value*
Wilhelmsson et al[26]	116	114	12.1	6.1	0.18
Ahlmark and Saetre[7]†	93	69	11.8	7.2	0.48
Barber et al[12]‡	147	151	31.3	27.2	0.51
Multicenter International Study[23]	1,520	1,533	8.4	6.7	0.051
Andersen et al[9]‡	242	238	26.2	25.2	0.92
Baber et al[11]	365	355	7.4	7.9	0.91
Norwegian Multicenter Study[22]	939	945	16.2	10.4	0.0003
BHAT[13]	1,921	1,916	9.8	7.2	0.005
Hansteen et al[18]	282	278	13.1	9.0	0.16
Julian et al[20]	583	873	8.9	7.3	0.32
Taylor et al[24]	471	632	10.2	9.5	0.78
Pindolol Study Group[10]	266	263	17.7	17.1	0.36
European Infarction Study[14]	880	861	5.1	6.6	0.14
Lopressor Invervention Trial[21]	1,200	1,195	5.2	5.5	0.90
Boissel et al[27]	309	298	11.0	5.7	0.013

*The p values computed for chi-square test comparing the proportion of deaths in each group.
†Incomplete reporting.
‡Mortality includes all in-hospital deaths.
BHAT = Beta Blocker Heart Attack Trial.
Adapted with permission from Frishman.[50]

a trial endpoint of total mortality or a clearly defined cause-specific mortality, a total sample size of at least 200, and random assignment of patients to either the β-blocker group or a concurrently followed control group; 14 of the 15 trials used a placebo-treated control group and included a double-blind phase. The time between the infarction and the start of β-blocker or placebo treatment ranged from <24 hours to 7.5 years.

The results from 12 of the 15 long-term trials showed a lower mortality rate in the β-blocker group compared with the placebo group (Table I).[7–10,12,13,18–20,22–27] In the 3 largest studies, the reduction in mortality with β blockade was statistically significant.[13,19,22,23] In the remaining 9 trials, the results were not always conclusive with regard to overall mortality.

In the 1990 Acebutolol et Prevention Secondaire de l'Infarctus (APSI) study, acebutolol, a β_1-selective adrenergic blocker with partial agonist activity, was compared with placebo in the prevention of late death in high-risk, post-acute MI patients.[27] There was a 48% decrease in overall mortality with acebutolol compared with placebo. The vascular mortality was reduced by 58%, the greatest benefit ever observed with a β blocker. The investigators concluded that moderately severe post-MI patients can benefit from a β blocker, and an agent having mild partial agonism can be effective.

Combining the results of all 15 β-blocker trials, overall mortality was reduced by approximately 22%, sudden death by 33%, nonsudden death by 20%, and nonfatal reinfarction by 20% with β-blocker therapy compared with placebo.[7–27] Retrospective analyses of the trials suggest that patients with non-Q-wave MI should benefit from β blockade similarly to patients with Q-wave MI.[28] Diabetic patients also appear to benefit from β-blockade post-MI.[29] Patients post-MI should avoid β-blocker withdrawal because of the increased risk of developing a new MI and/or unstable angina pectoris.[30]

BETA-ADRENERGIC BLOCKADE IN THE EARLY PHASE OF MYOCARDIAL INFARCTION

Beta-adrenergic blockers have been considered for use as standard therapy in patients with hyperacute MI to prevent the undesirable consequences of increased sympathoadrenal discharge: coronary artery rethrombosis, arrhythmias, and extension of myocardial injury.[6] The Metoprolol in Acute Myocardial Infarction (MIAMI) study set out to evaluate the effect of metoprolol on mortality in patients entering the hospital <24 hours after the onset of chest pain.[31] Included in the study were 5,778 patients considered to be in a low-risk category (patients with bradycardia, hypotension, and left ventricular failure were excluded). Patients received either placebo or intravenous metoprolol (15 mg) followed by oral metoprolol for 15 days. A nonsignificant reduction in mortality of 13% was observed. Retrospective subgroup analysis suggested that an older population of patients with

associated risks (previous angina, previous infarction, diabetes) experienced a 29% reduction in mortality.

The First International Study of Infarct Survival (ISIS-1) was a large, open, randomized investigation designed to establish the effect of short-term atenolol treatment on total mortality and cardiovascular mortality at 1 week and 1 year after the onset of chest pain.[32] Intravenous atenolol 5–10 mg was administered and followed by oral atenolol 100 mg daily for 1 week. Of patients at low risk, >16,000 were studied; 80% were admitted to the study within <8 hours after onset of chest pain. A significant reduction in cardiovascular mortality of 15% was observed with atenolol therapy. The benefit was confined to the first 36 hours. The reduction in mortality on days 0–1 was 32%.

Patients in the ISIS-1 were followed for 1 year.[32] The cardiovascular mortality was 10.1% in the atenolol group and 11.3% in the control group, representing a 10.6% reduction in mortality. The extra lives saved during days 8–365 most likely were related to intravenous β-blocker administration because, at hospital discharge, more patients in the atenolol group than in the control group remained on β-blocker therapy (35% vs 26%).

An early intervention study in 1,395 MI patients randomized to receive either intravenous metoprolol followed by 200 mg/day orally or placebo for 3 months showed that the significant early benefit in mortality reduction at 90 days was still present 2 years later.[33] The benefit, however, was not present 5 years later.[34]

The addition of β blockers to acute thrombolytic therapy in MI may improve patient outcome to a greater extent than either treatment used alone.[35] This was suggested by the favorable findings of the Second Thrombolysis in Myocardial Infarction (TIMI-II) study in which metoprolol was combined with recombinant tissue plasminogen activator (rt-PA) in patients with MI.[36]

MECHANISMS OF BENEFIT

An analysis of cause-specific mortality in the acute and long-term β-blocker MI trials indicates that the reductions in total mortality were caused by reductions in cardiovascular deaths.[4] An antiarrhythmic mechanism is suggested for this benefit because β blockers have been shown to reduce the incidence of sudden cardiac death, numbers of ventricular premature contractions, and episodes of ventricular tachycardia compared with placebo treatment.[2]

Although different definitions of sudden death were reported in the trials, a large part of the benefit from β-blocker therapy appears to have stemmed from the prevention of these deaths.[4,5,15] Eight trials reported on sudden death; the rates of sudden cardiac death were lower in the β-blocker group for all 8 trials.[15,27] Beta-blocker treatment appears to manifest a trend toward a greater overall reduction in sudden cardiac death than in all-cause mortality.

In 3 trials reporting on sudden death, 24-hour ambulatory electrocardiographic (ECG) records were obtained of a subset of participants, both at trial entry and at a subsequent follow-up visit.[13,20,21] The findings of these trials are similar. In the subgroup of survivors who entered the trial with frequent ventricular premature beats, fewer patients demonstrated this type of arrhythmia at a later follow-up visit compared with the placebo groups.[20,37,38] Among patients with frequent ventricular premature beats at entry, many continued to have this type of arrhythmia at follow-up, although fewer of these patients were on β blockers than on placebo. Although the recorded episodes of ventricular tachycardia were few in all trials at follow-up, this arrhythmia was less common in patients receiving β blockers than in those receiving placebo.

In the trials, a higher serum potassium concentration and a shorter corrected ECG QT interval were noted in patients receiving β blockers compared with placebo.[2] Beta blockers have been observed to attenuate transmembrane potassium fluxes in response to high catecholamine levels.[39] Perhaps part of the protective effect of β blockade derives from an ability to preserve normal serum potassium levels, especially in those patients receiving concurrent diuretic therapy.[40]

The known anti-ischemic actions of β blockers may also have contributed to their beneficial effects in the postinfarction period. Stimulation of cardiac β-adrenergic receptors by endogenous catecholamines increases myocardial oxygen consumption and can thereby aggravate the ischemic process. Beta blockers reduce myocardial oxygen requirements by blunting the effects of catecholamines on blood pressure, heart rate, and myocardial contractility.[41] The effects of these drugs on coronary blood flow are less well-defined.

Beta blockers may decrease coronary blood flow by allowing the unopposed influence of coronary vasoconstrictor impulses to prevail. These drugs may also augment or maintain overall coronary blood flow by slowing the heart rate and increasing diastolic perfusion time.[4,5]

An intriguing anti-ischemic mechanism for the

beneficial effect of β blockers is the possibility that these agents might prevent the atherosclerotic plaque tears and fissures that are probable causes of coronary thrombosis.[2,28] Coronary thrombi, large enough to be detected by angiography, are often associated with tears (fissures) in the caps of atherosclerotic plaques.[42,43] These tears allow blood to penetrate into the arterial wall, leading to thrombus formation within the intima; this may be followed by propagation of thrombosis into the vessel lumen.

Why a plaque becomes susceptible to rupture is not known. It has been proposed that sudden increases in blood pressure and/or myocardial contractility related to adrenergic stimulation could cause a vulnerable atherosclerotic plaque to crack in a coronary artery with the subsequent propagation of a thrombus.[44] It is proposed that β blockers might reduce the risk of plaque rupture and its consequences by attenuating the effects of catecholamines on blood pressure, contractility, and platelet activation. Aspirin, and perhaps β blockers with their antiplatelet effects, possibly protects against the propagation of thrombosis once a plaque rupture occurs. Studies need to be done to test this hypothesis.

Beta blockers are known to protect a vulnerable aorta from acute dissection, as well as to reduce the risk of recurrent dissection.[1] This is accomplished, in part, by the ability of β blockers to reduce blood pressure and myocardial contractility. Studies using Doppler ultrasonography demonstrated that propranolol was more likely than hydralazine to reduce both the velocity of blood flow and the likelihood of nonlaminar blood flow in the aorta.[45] This effect of β blockade could reduce the risk of endothelial damage and plaque rupture; subsequent coronary thrombosis would be less likely to occur. In addition, some β blockers also have weak antiplatelet effects that might prevent the propagation of clots.[46] Other possible mechanisms of benefit with β blockade include favorable effects on myocardial metabolism, renin-inhibiting actions, and improvements in coronary collateral flow and oxygen–hemoglobin dissociation.[41,42]

CONCLUSION

Evidence suggests that among the drugs available for treatment of hypertension and ischemia, β blockers may be especially useful. These agents have been shown to reduce the incidence of total mortality, cardiovascular mortality, sudden death, and nonfatal reinfarction in survivors of acute MI. Beta blockers are also useful for reducing mortality during the hyperacute phase of MI when administered parenterally with and without thrombolysis.

The protective effects of β blockade probably extend beyond their antiarrhythmic activity and ability to reduce determinants of myocardial oxygen demand. Beta blockers appear to have important antithrombotic properties not related to direct anticoagulant activity but possibly related to indirect means in reducing the risk of coronary artery plaque rupture and the eventual propagation of thrombosis. As evidence continues to mount regarding the circadian variation of acute cardiovascular events, the importance of maintaining pharmacodynamic action over 24 hours may become paramount.[47]

Studies suggest that the greatest benefit from β-blocker therapy is achieved in patients who are >60 years of age and in the medium-to-high risk postinfarction population (patients with left ventricular dysfunction and/or arrhythmias).[5,6,27,48] Trials investigating 10 different β blockers found favorable mortality trends, suggesting that the benefit is conferred by the drug class rather than by a specific β blocker.

A new controlled-release formulation of metoprolol (95 mg) for hypertension and angina pectoris, available for some time in Europe, has recently been approved for use in the United States by the Food and Drug Administration.[49] This formulation produces steady-state plasma concentrations that vary less throughout the day than they do with a conventional 100 mg once-daily tablet formulation of metoprolol. The controlled-release formulation has been noted to produce a more constant effect than immediate release formulations on exercise-induced tachycardia. A theoretical advantage to this formulation exists with regard to cardioprotection, since a lesser degree of fluctuation in drug plasma concentrations over 24 hours could sustain the favorable pharmacologic effects of β blockade. This formulation, however, is not yet approved as a postinfarction agent.

Used in conjunction with coronary disease risk-factor management, aspirin, and other pharmacologic agents, β blockers appear to be an important component of a rational approach for reducing the incidence of mortality and morbidity in patients who have survived MI.

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Calcium Antagonists as Cardioprotective Agents

Edward D. Frohlich, MD

The potential role that calcium antagonists play toward enhancing cardioprotection is discussed, while recognizing that they are much more heterogeneous than other classes of antihypertensive or antianginal agents. Similarities and differences between the mechanisms of action and clinical effects of individual drugs are discussed. Among these is the ability of some of them to reduce left ventricular hypertrophy rapidly while simultaneously and uniquely increasing right ventricular wall thickness. Although the clinical importance of this as a potential cardioprotective effect is undetermined, the renal protective effect of some calcium antagonists is discussed in detail.

(Am J Cardiol 1992;70:7 I–9 I)

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The pharmacologic effects of the calcium antagonists were first characterized by Fleckenstein[1] in 1958. In describing the effects of verapamil, Fleckenstein noted reduction of arterial pressure, a negative myocardial inotropic effect, and a slowing of heart rate. These properties suggested that the compound was a β-adrenergic receptor blocker until further studies elucidated a new class of agents, the calcium antagonists.[1]

The calcium antagonists were initially introduced in the United States for the treatment of angina pectoris and supraventricular tachycardia. Later, they were approved for the treatment of hypertension—another resemblance to the β blockers. Although these agents are effective in the treatment of coronary artery disease and hypertension, other cardioprotective effects of these agents, through their antiatherosclerotic actions, have been reported in experimental animal models.

The calcium antagonists, a growing class of compounds, are extremely heterogeneous. Members of this class that are now available or under clinical investigation in the United States are listed in Table I. These agents are far more heterogeneous than the other classes of antihypertensive agents; this is related to their structural and chemical properties as well as to their pharmacologic and physiologic characteristics. The first 3 compounds in this class that were introduced, verapamil, diltiazem, and nifedipine, have been most extensively investigated with respect to their antihypertensive and antianginal properties. However, not every calcium antagonist reduces arterial pressure; nimodipine, for example, is used for patients with cerebral bleeding and does not reduce pressure.

The calcium antagonists act by inhibiting the entrance of calcium ions (Ca^{2+}) into cells and reducing intracellular Ca^{2+} availability. At least 4 types of calcium channel receptors are known to exist at the cell membrane; calcium antagonism is thought to be achieved principally through the inhibition of the L (slow, or long acting) channel and through inhibition of release of Ca^{2+} from intracellular stores in the sarcoplasmic reticulum, mitochondria, and from binding to proteins (including calmodulin).[1,2] Each of these mechanisms pro-

TABLE I List of Calcium Antagonists in Clinical Study and Practice in the United States

Amlodipine	Nicardipine
Clentiazem	Nifedipine
Diltiazem	Nisoldipine
Felodipine	Nimodipine
Gallopamil	Nitrendipine
Isradipine	Verapamil

vides the means of calcium antagonism and thereby a reduced state of contractility of the cardiac or vascular myocyte. Further, the calcium antagonists may operate through inhibition of >1 calcium channel or other receptor or through the Ca^{2+} release mechanism. Nifedipine, for example, also operates at the α-adrenergic receptor in addition to its action at its calcium channel receptor.

The different effects and related mechanisms of the various calcium antagonists are responsible for considerable variability in their clinical actions. Thus, understanding the differences in their dilating effects in various blood vessels and the heart is critical to understanding the multiplicity of their cardiovascular and renal protective effects.

The first report concerning the hemodynamic effects of the calcium antagonist nifedipine in hypertensive patients was by Olivari et al.[3] They reported that after 3 weeks of treatment, mean arterial pressure was reduced through a decrease in total peripheral resistance. Similar systemic hemodynamic effects have been reported for diltiazem,[4] verapamil,[5] and other calcium antagonists. Following their intravenous administration, all 3 agents are associated with a reflexive increase in heart rate, cardiac output, and myocardial contractility accompanied by increased circulating levels of norepinephrine.[4,5] Variable systemic effects on heart rate and cardiac output may be seen with more prolonged therapy. Reduction in arterial pressure has not been related to expanded intravascular (plasma) volume or alterations in the renin–angiotensin–aldosterone system.[3–5]

Despite this seeming similarity in the systemic hemodynamic effects of these agents, their renal hemodynamic effects are more variable. Although all 3 agents (nifedipine, diltiazem, and verapamil) maintain glomerular filtration rate and reduce renal vascular resistance,[3–5] only diltiazem decreases the renal filtration fraction.[4,6] This is achieved through efferent as well as afferent glomerular arteriolar dilation, thereby reducing intraglomerular hydrostatic pressure.[6] Using micropuncture techniques in the spontaneously hypertensive rat, we have confirmed the calculated intrarenal hemodynamic changes originally reported in humans.[6] Thus, the diminished efferent arteriolar resistance allows glomerular hydrostatic pressure to diminish. By reducing glomerular hydrostatic pressure, diltiazem may be able to protect the kidney from the glomerular hyperfiltration and glomerulosclerosis that complicates essential hypertension.[7]

More recently, we have augmented these clinical hemodynamic findings by demonstrating their effects on the heart.[8] We found that, although the calcium antagonists rapidly diminish left ventricular (LV) mass in rat and humans,[4–6] they simultaneously increase right ventricular wall thickness.[8] In this recent echocardiographic study comparing 6 calcium antagonists and 3 angiotensin-converting enzyme (ACE) inhibitors, all 9 agents reduced LV mass, posterior wall thickness, and septal wall thickness; but only the calcium antagonists (all 6) increased right ventricular wall thickness. These findings strongly suggest that both classes of antihypertensive drugs have similar systemic hemodynamic effects, but they act through different nonhemodynamic mechanisms on the mass of the 2 ventricles.

The mechanism for the independent risk of increased cardiovascular morbidity and mortality that is associated with LV hypertrophy is not yet known.[9] In all likelihood, hemodynamic and also nonhemodynamic factors contribute in the development and reversal of hypertrophy. All antihypertensive agents will reduce cardiac mass if they are used long enough, but only certain classes of these drugs rapidly reduce LV mass with short-term therapy.[10] This most likely reflects their nonhemodynamic actions. It is not known yet why these antihypertensive drugs have differing effects on cardiac mass.

The calcium antagonists reduce arterial pressure by decreasing arteriolar smooth muscle tone. This is achieved by decreasing the availability of intracellular calcium ions for muscle contraction. The persistent decrease in arterial pressure is achieved by a reduction in total peripheral vascular resistance, which is shared by all the major vascular territories. Only certain calcium antagonists increase renal blood flow and this is not accompanied by increased glomerular hydrostatic pressure and filtration rate, a genuine renal protective effect. Although calcium antagonists reduce LV mass, they do so through mechanisms that seem to be distinct from other antihypertensive drugs.

Studies concerned with the LV mass-reducing effects of calcium antagonists are ongoing but no

study has yet demonstrated reversal of the risk associated with LV hypertrophy. Current experience suggests that certain subsets of patients with essential hypertension can derive particular benefit from calcium antagonist therapy. Black or older hypertensive patients, and those with volume-dependent hypertension and lowered plasma renin activity in particular, may benefit from the calcium antagonists. Other patients who may benefit from treatment with these agents include patients with angina pectoris who are not fully responsive to β blocker therapy and patients with bilateral renal arterial disease (or unilateral disease with a solitary kidney) in whom the ACE inhibitors are contraindicated. Finally, the calcium antagonists may also be the appropriate therapy for those patients who have experienced metabolic alterations with other classes of antihypertensive therapy. Clearly, additional studies are necessary to demonstrate their additional cardiovascular and renal protective effects.

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Angiotensin-Converting Enzyme Inhibitors as Cardioprotective Agents

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This discussion of documented and possible cardioprotective effects of angiotensin-converting enzyme (ACE) inhibitors examines the variety of sites along the pathway to end-stage heart disease at which they might intervene. In addition to their antihypertensive activity, their effects on left ventricular hypertrophy, lipid profiles, and insulin sensitivity are discussed in comparison to the effects of other classes of antihypertensive agents on these risk factors. The ability of ACE inhibitors to prevent the progression of congestive heart failure and reduce mortality is documented and a summary of data demonstrating benefits of their use in postmyocardial infarction patients with low ejection fraction is presented.

(Am J Cardiol 1992;70:10 I–17 I)

Cardioprotection can be achieved through intervention at different points along the pathway to end-stage heart disease (Figure 1).[1] The most desirable stage for intervention is very early, through the reduction of risk factors and the prevention of atherosclerosis and left ventricular (LV) hypertrophy, which are the leading causes of cardiovascular complications. Once cardiovascular disease is present, however, there is still room for cardioprotection. Thus, in the patient with manifest atherosclerosis or hypertension, the goal would be to prevent myocardial infarction and to prolong survival. Even in patients with postmyocardial infarction or congestive heart failure (CHF), there is potential to prevent reinfarction and death.

Cardioprotection can be both primary and secondary in nature. *Primary* cardioprotection is defined as the prevention of cardiovascular disease. A *definite* primary cardioprotective effect would be the prevention of cardiac deaths in persons without manifest cardiovascular disease. *Probable* primary cardioprotection would be demonstrated by a reduction of surrogate endpoints of disease, such as prevention of LV hypertrophy or atherosclerosis and their complications. *Secondary* cardioprotection is demonstrated by reductions in mortality, morbidity, and recurrent events in persons with established cardiovascular disease. It is in the area of secondary cardioprotection that more data are available with regard to both long-term and acute cardioprotective interventions.

Angiotensin-converting enzyme (ACE) inhibitors can intervene in the pathway to end-stage heart disease, and therefore ACE inhibitors can be considered as cardioprotective agents. Although definite primary cardioprotection has not been proven with ACE inhibitors, data are available to support a probable primary cardioprotective effect of these agents.

PRIMARY CARDIOPROTECTION WITH ACE INHIBITORS

Prevention or limitation of atherosclerosis: The large proportion of the population with essen-

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tial hypertension is an ideal target for cardioprotective therapy. Hypertension is associated with an increased risk of morbid and fatal cardiovascular events, and this risk increases markedly when very high levels of blood pressure and other risk factors are present.[2,3] These complications can be reduced with effective antihypertensive therapy.[4,5] This is especially true for stroke and heart failure but less impressive for myocardial infarction and death due to coronary artery disease. Although recent trials in high-risk older patients do show reduction in these latter complications,[6–8] most of these trials relied on diuretic-based therapy and it can be questioned whether this provides optimal cardioprotection. Since atherosclerotic disease plays a major role in these complications, cardioprotective antihypertensive therapy must prevent the progression of atherosclerosis or, ideally, reverse it. In any case, it should not accelerate this process.

Over the years, some antihypertensive drugs have been shown to affect lipid profiles adversely, suggesting that these agents may neither reverse nor prevent atherosclerosis.[9,10] With respect to lipid effects, an ideal drug would reduce total cholesterol, low-density lipoprotein (LDL) cholesterol, and perhaps also triglycerides, while increasing high-density lipoprotein (HDL) cholesterol. Among antihypertensive agents, the α-adrenergic blocking drugs come closest to this ideal. These agents, however, are not well tolerated by many patients. By causing an increase in heart rate and preferentially dilating the subepicardial coronary circulation, which may lead to a coronary steal, α blockers may worsen the balance between myocardial oxygen demand and supply.[11]

ACE inhibitors are among the agents with no adverse effect on plasma lipids and therefore should not exacerbate atherosclerosis. Indeed, experimental data suggest a potential for the opposite effect. In hyperlipidemic rabbits, 9 months of treatment with the ACE inhibitor captopril led to a significant reduction in aortic atherosclerosis, as shown in Figure 2.[12]

The antiatherosclerotic effect of captopril may be largely related to its antihypertensive action, which could reduce the transport of lipids into and beyond the intima or decrease the activity of the atherosclerotic plaques. It is also possible that ACE inhibitors have a specific action related to their ability to inhibit the vascular renin–angiotensin system, which may be involved in vessel wall changes.[13] Certainly, an antiatherosclerotic action would go a long way toward making the ACE inhibitors successful primary cardioprotective agents, but further experimental and clinical confirmation is required.

Prevention or regression of LV hypertrophy: LV hypertrophy has been recognized as a marker for cardiovascular risk for many years. In the original reports from the Framingham Heart Study,[14] LV hypertrophy seen on the electrocardiogram was found to be the most powerful indicator for cardiovascular morbidity and mortality. Hypertension correlated as the leading cause of LV

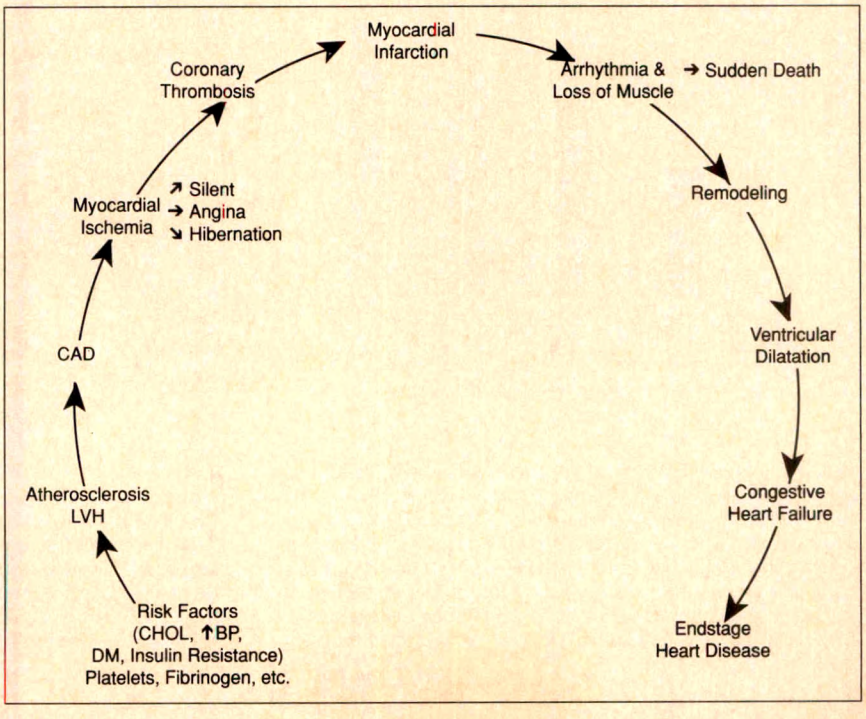


FIGURE 1. The chain of events in coronary artery disease (CAD) that lead from risk factors to preclinical vascular and myocardial abnormalities, coronary events, congestive heart failure, and death. BP = blood pressure; CHOL = cholesterol; DM = diabetes mellitus; LVH = left ventricular hypertrophy. (Reprinted with permission from *Am Heart J.*[1])

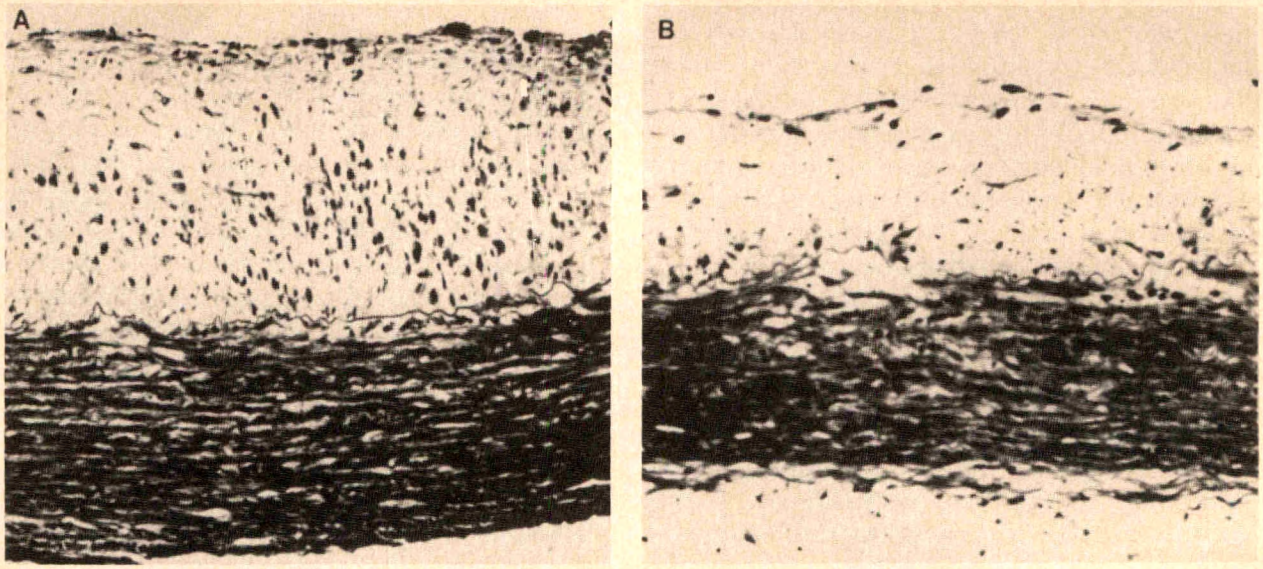


FIGURE 2. *A*: Photomicrograph of cross section through atherosclerotic plaque in descending thoracic aorta of a 12-month-old untreated Watanabe heritable hyperlipidemic (WHHL) rabbit. This area was evaluated visually as an "advanced lesion." Note cellularity of intimal lesion and thickness of media. (Hematoxylin-eosin; original magnification × 150.) *B*: Photomicrograph of cross section through atherosclerotic plaque in descending thoracic aorta of a 12-month-old WHHL rabbit after 9 months of captopril treatment. Section taken from area evaluated visually as an "advanced lesion." Note sparse cells, occasional calcium granules, and somewhat thinner media than in A. (Hematoxylin-eosin; original magnification × 150.) (Reprinted from *Hypertension*.[12])

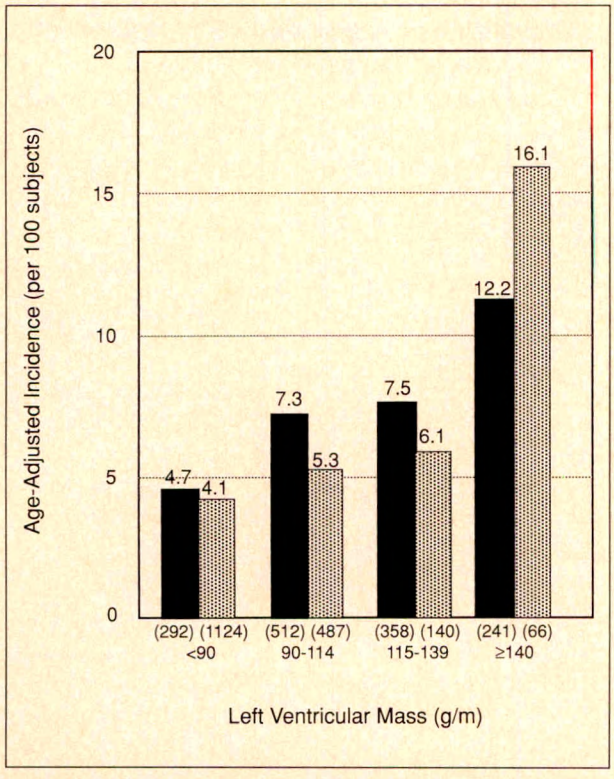


FIGURE 3. Four-year age-adjusted incidence of cardiovascular disease, according to left ventricular mass (corrected for height). The numbers in parentheses indicate the numbers of subjects at risk. The rates for men are represented by black bars and those for women, by stippled bars. The 4 corresponding categories based on left ventricular mass corrected for body surface area are <75, 75–94, 95–116, and >116 g/m^2. (Reprinted with permission from *N Engl J Med*.[16])

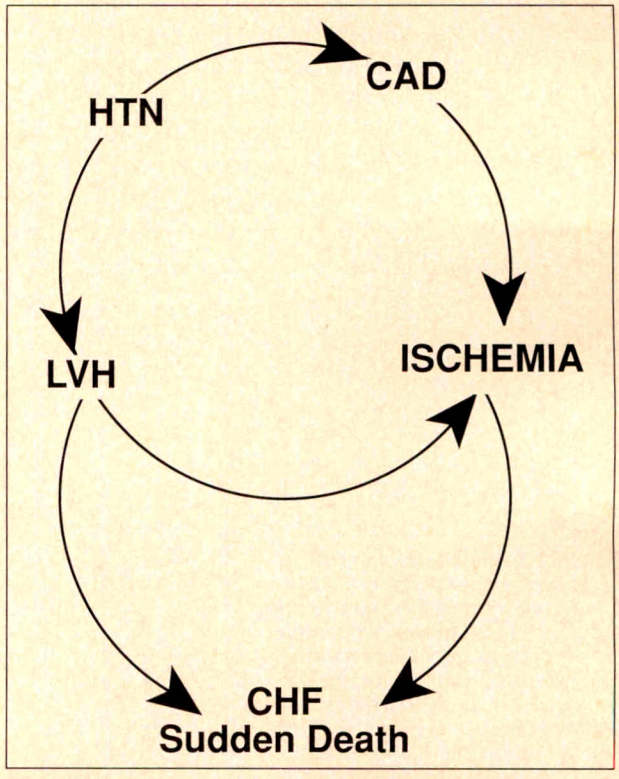


FIGURE 4. Schema of the probable interrelations between hypertension (HTN), left ventricular hypertrophy (LVH),and the various manifestations of hypertensive heart disease. The probable synergism between left ventricular hypertrophy and myocardial ischemia related to coronary artery disease (CAD) is emphasized and is likely to be responsible for many of the cases of congestive heart failure (CHF) and sudden death. (Reprinted with permission from *J Cardiovasc Pharmacol*.[17])

hypertrophy, but of all the hypertensive patients, only a small number of patients were thought to have LV hypertrophy. With the availability of echocardiography, however, LV hypertrophy has been found to be much more common, affecting 10–50% of hypertensive populations. Echocardiographically demonstrated LV hypertrophy remains a strong predictor of future cardiovascular events.[15,16] Increasing LV mass is associated with a progressive increase in age-adjusted cardiovascular disease (Figure 3). This relation is partially independent of blood pressure.

Although it is clear that LV hypertrophy is a marker of risk, there is also good reason to suggest that it plays a causal role as well (Figure 4).[17,18] LV hypertrophy is associated with a diminution of coronary vascular reserve, both in animal models and in humans.[19–21] Under conditions of increased myocardial demand or reduced perfusion, these abnormalities may lead to subendocardial ischemia. More importantly, LV hypertrophy may provide a substrate that enhances the risk and resulting damage from accompanying coronary artery disease.[22,23] LV hypertrophy also is commonly associated with LV diastolic dysfunction,[24] which may lead to symptoms of heart failure and probably is responsible for the increased occurrence of atrial fibrillation in hypertension. In animal models, and probably also in humans, chronic and severe LV hypertrophy may lead to systolic dysfunction.[25–27] Finally, ventricular arrhythmias are more common in patients with LV hypertrophy, especially when coronary artery disease is also present (Figure 5).[28]

The effect of antihypertensive regimens on LV mass has been studied in experimental animals and in humans. It is clear that effective antihypertensive therapy can prevent or reverse LV hypertrophy.[29,30] It is uncertain, however, whether this effect is related to blood pressure control alone or is also dependent on the mechanism of action of the medications employed.[31] The sympathetic nervous system, the renin–angiotensin system, and calcium ions (Ca^{2+}) are all factors that have been thought to play a role in the development of LV hypertrophy. Agents that block or modify these factors, therefore, have been considered logical treatments to maximize regression of LV hypertrophy. Unfortunately, the data are not conclusive, and the ability of diuretic-based therapy to reverse LV hypertrophy has also been repeatedly demonstrated, especially in long-term trials. Nonetheless, the literature indicates that ACE inhibitors consistently regress LV hypertrophy at least as much as other antihypertensive agents (Figure 6).[29,30]

If the ACE inhibitors do have a specific effect on regression of LV hypertrophy, it may be explained by the evolving understanding of the effect of angiotensin II on myocyte growth.[32] Angiotensin II, via stimulation of specific receptors, activates 2 secondary messengers, diacylglycerate and inositol triphosphate, which in turn lead to increased intra-

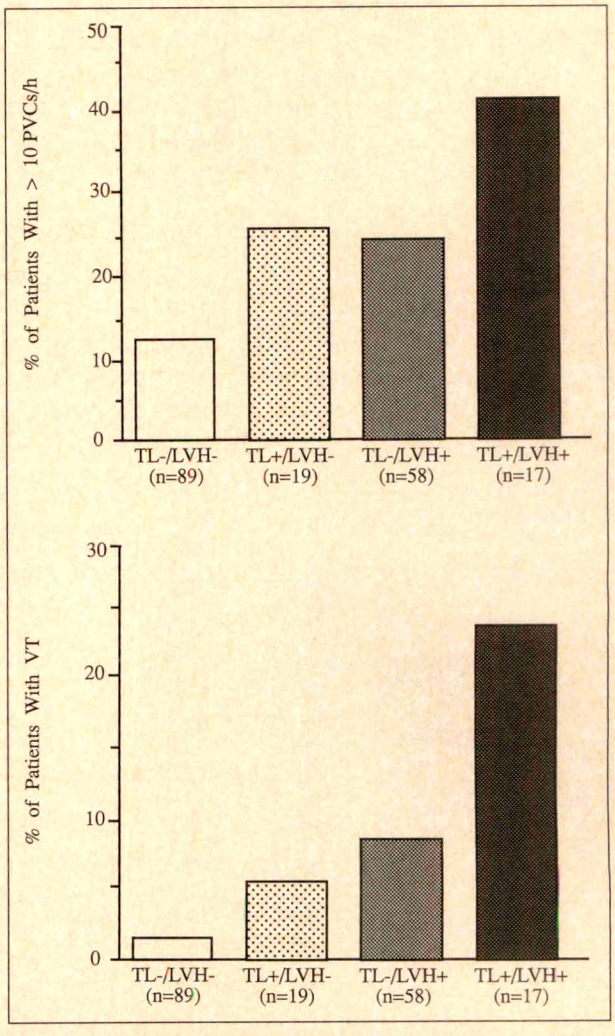


FIGURE 5. ***Top*: The number and percent of patients with frequent (≥10/hour) premature ventricular complexes (PVCs) are shown for 4 groups: those with both a negative thallium-201 scintigram (TL−) and a left ventricular mass index <134 g/m² (LVH−), those with a reversible scintigraphic defect (TL+) and no left ventricular hypertrophy (LVH−), those with no thallium defect (TL−) and a left ventricular mass index ≥134g/m² (LVH+), and those with a thallium defect and left ventricular hypertrophy (TL+, LVH+). The prevalence of frequent premature ventricular complexes increases when 1 or both tests are positive (p <0.03 by chi-square analysis).** ***Bottom*: The same format is used to show the number and percent of patients with nonsustained ventricular tachycardia (VT). Again, arrhythmias are more common when ≥1 tests are abnormal (p <0.005). (Reprinted with permission from *J Am Coll Cardiol*.[28])**

cellular Ca^{2+} and the activation of a number of growth factors. The growth factors activated by the diacylglycerate pathway appear particularly important in myocardial growth and hypertrophy. This may be the explanation for the disproportionate effect of ACE inhibitors on LV hypertrophy, if it is confirmed.

ACE inhibitors may also be unique in their effect on the cardiac interstitium. Increased collagen and alterations in the distribution and composition of collagen accompany the evolution of LV hypertrophy.[33,34] These abnormalities may be more resistant to reversal than myocyte hypertrophy and may be responsible for the pathophysiologic abnormalities accompanying LV hypertrophy. ACE inhibitors appear to be able to prevent or reverse these changes.[35]

The effects of insulin (and the insulin resistance that characterizes many hypertensive patients) on lipid metabolism, vascular hypertrophy, and cardiac hypertrophy are other areas of active research. Persons with hypertension tend to be insulin resistant,[36] and the effects of antihypertensive therapy on insulin sensitivity may represent another potential marker for the prevention of atherosclerosis. Diuretics and some β blockers produce an increase in insulin resistance in hypertensive nondiabetic patients, whereas ACE inhibitors have been found to have either no effect or perhaps cause some increase in insulin sensitivity.[37] As with their potential antiatherosclerotic actions, however, the clinical significance of insulin resistance and its relation to ACE inhibition need to be clarified.

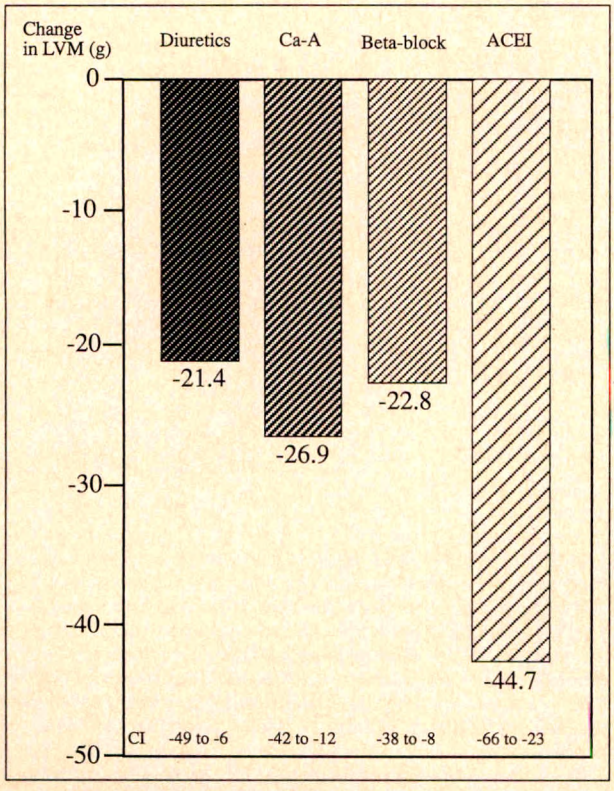


FIGURE 6. Absolute changes and 95% confidence intervals (CIs) in left ventricular mass (LVM), calculated according to the Penn cube formula from original data given in each study when available. Changes have been adjusted for differences between studies (analysis of covariance). ACEI = angiotensin-converting enzyme inhibitor; Beta block = beta blocker; Ca-A = calcium antagonist. (Reprinted with permission from *Am J Hypertens*.[30])

Secondary cardioprotection with ACE inhibitors: More data are available to support the effectiveness of ACE inhibitors for secondary than for primary cardioprotection. Two conditions in which ACE inhibitors have been demonstrated to be cardioprotective are CHF and postinfarction LV dysfunction.

Cardioprotection by ACE inhibitors in congestive heart failure: Several years ago, the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS) showed that enalapril prolonged survival and prevented hospitalizations in end-stage CHF (refractory New York Heart Association [NYHA] class IV) patients.[38] The more recently published Studies of Left Ventricular Dysfunction (SOLVD) treatment trial examined ambulatory patients with mild-to-moderate CHF.[39] In the SOLVD trial, 2,569 patients with symptomatic NYHA class II and III heart failure and an impaired LV ejection fraction were randomized to receive either enalapril (mean dose 16 mg/day) or placebo.

The effects of therapy on mortality and the number of hospitalizations were examined during a follow-up period of 22–55 months (mean 41 months). Overall, a 16% reduction in mortality was observed in the ACE inhibitor treatment group relative to placebo. In virtually all subsets of the study population, e.g., patients with different grades of heart failure and varying reductions in LV ejection fraction, reductions in mortality and prevention of disease progression, as shown by the reduction of hospitalizations, were observed (Figure 7).

Given the efficacy with which ACE inhibitors prevent the progression of symptomatic CHF, one would hope that even earlier intervention might prevent CHF. The SOLVD prevention trial addressed this question, randomizing 4,226 patients with LV dysfunction (ejection fraction $\leq 35\%$) but without CHF symptoms or the requirement for specific therapy to enalapril or placebo.[40] The ACE inhibitor group had a lower rate of hospitalization for CHF or new onset CHF. Mortality tended to be lower in the enalapril group, and the survival

curves in patients who developed CHF appeared to be similar to those in the treatment trial. Thus, strong evidence supports the benefit of ACE inhibitor therapy in all grades of CHF and LV systolic dysfunction.[41] This approach protects against the onset of CHF, its progression, and death from CHF.

Cardioprotection by ACE inhibitors of post-myocardial infarction: In an elegant series of studies, Pfeffer and colleagues[42,43] showed that captopril prevented LV dilation, evolution of heart failure, and death in rats with infarction induced by left anterior descending coronary artery ligation. Whether this was due to unloading resulting from the hemodynamic effect of ACE inhibition or to inhibition of a specific action of the renin–angiotensin system is unclear.[44]

There is ample reason to expect, however, that prevention of LV dilation and thinning and dysfunction of the myocardium surrounding the infarct zone should improve subsequent prognosis. It was clearly demonstrated in several studies in which patients after myocardial infarction were followed over the subsequent year that ACE inhibitors can prevent this remodeling process.[45,46]

The Survival and Ventricular Enlargement Trial (SAVE) was designed to test this hypothesis by studying >2,000 patients with an ejection fraction ≤40% and no overt CHF. They were randomly assigned to receive either captopril or placebo commencing 3–16 days postinfarction. The results, which were recently presented but remain unpublished, showed that captopril reduced endpoints, including onset of CHF, hospitalizations, and deaths from CHF, by 16–20%.[47] This benefit was seen in virtually all patient subgroups, including patients who did or did not receive thrombolytic therapy, β blockers, and coronary revascularization.

As in the SOLVD trial, there were also 24% fewer subsequent infarctions and less frequent episodes of unstable angina in the ACE inhibitor group. The mechanism by which ACE inhibitors accomplish this effect is not clear. In any case, ACE inhibitors appear to be indicated in postinfarction patients with substantial LV dysfunction.

Other possible cardioprotective effects of ACE inhibitors: Additional data suggest that ACE inhibitors may be useful as cardioprotective agents in the acute myocardial infarction setting. Potential mechanisms include their beneficial hemodynamic effects, protection against oxygen free radical damage (possibly limited to sulfhydryl-containing agents, such as captopril),[48] or an undefined action. In rat and canine models of myocardial infarction, ACE inhibition commenced prior to or at the time of infarction decreased the size of the infarction.[49–51] In a dog model, a reduction in the incidence of ventricular fibrillation immediately after myocardial infarction has been demonstrated when ACE inhibitors were given prior to occlusion or during reperfusion subsequent to myocardial infarction.[52] The reduction in ventricular fibrillation may in part result from prevention of reperfusion damage. Preliminary data suggest that concomitant captopril administration and thrombolytic therapy may have an additive, beneficial effect postinfarction.[53] This may also reflect prevention of reperfusion injury.

Experimental evidence suggests that ACE inhibitors may possibly protect the heart through an effect on energy metabolism during ischemia. In the perfused rat heart, pretreatment with ramiprilat, the active metabolite of the ACE inhibiting agent ramipril, prevented depletion of glycogen, adenosine triphosphate, and creatinine, while preventing the accumulation of lactate.[54]

A very exciting area of current research concerns the effects of ACE inhibitors on vascular biology and endothelial responses in vascular smooth muscle. In an animal model of vascular injury, ACE inhibition treatment prevented the subsequent proliferative response.[55] In a large retrospective study of patients undergoing percutaneous transluminal coronary angioplasty, patients receiving enalapril or captopril at hospital discharge for either hypertension or heart failure had a markedly lower incidence of restenosis versus patients who did not receive ACE inhibitor therapy.[56] This has not been confirmed by prospective trials, however.

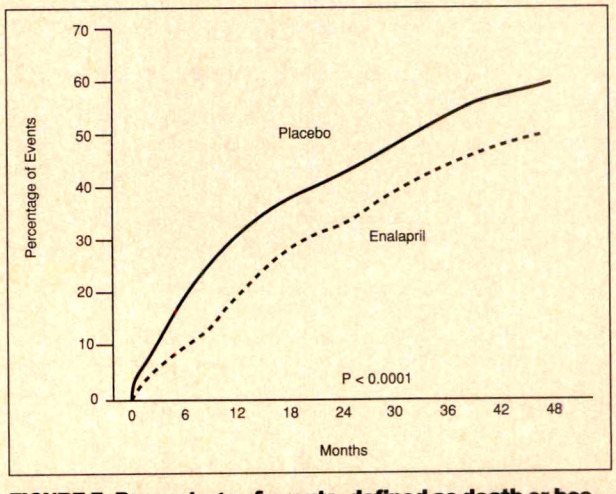


FIGURE 7. Percentage of events, defined as death or hospitalization for congestive heart failure, occurring in the placebo and enalapril groups in the SOLVD treatment trial. (Reprinted with permission from *N Engl J Med*.[39])

CONCLUSION

Ample evidence supports varied cardioprotective actions of ACE inhibitors at many points along the pathway to end-stage heart disease. These agents decrease blood pressure and prevent or regress LV hypertrophy. They do not adversely alter blood lipid profiles and may in fact have a beneficial effect on atherosclerosis. ACE inhibitor treatment at the time of a myocardial infarction may decrease infarct size and prevent arrhythmia. More certainly, these agents alter the remodeling process, resulting in LV dilation, thereby preventing progression to heart failure. In patients with LV dysfunction and failure, ACE inhibitor therapy may unexpectedly prevent myocardial infarction. Finally, and most conclusively, in patients with asymptomatic systolic dysfunction or symptomatic CHF, ACE inhibitors prevent the onset or progression of CHF and prolong survival.

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Thrombolytic, Antiplatelet, and Antithrombotic Agents

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The relative efficacy and safety of individual thrombolytic agents, administered alone and with antiplatelet and antithrombotic drugs, in the treatment of acute myocardial infarction are presented. The clinical benefits and risks of treatment choices are discussed in relation to the mechanisms of the formation and prevention of thrombus and thrombolysis. It is concluded that streptokinase, tissue plasminogen activator (t-PA), and anisoylated plasminogen-streptokinase activator complex (APSAC) significantly reduce mortality and improve left ventricular function equally, despite differences in the rate at which they achieve vascular patency, their durations of action, and the extent to which their use is associated with adverse events. The questions of how best to minimize reocclusion/reinfarction, bleeding, and stroke are discussed, with particular focus on the beneficial use of aspirin and the unresolved issue of how best to use heparin.

(Am J Cardiol 1992;70:18 I–26 I)

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The mechanism of acute myocardial infarction (MI) is a ruptured atherosclerotic plaque, exposing collagen fibers that bind platelets and initiate the coagulation cascade.[1] Platelets contain multiple receptors for various proteins that cause further platelet aggregation and adhesion (Figure 1).[2] Platelet membranes also bind coagulation Factors V and X, which potentiate conversion of prothrombin to thrombin. Thrombin, in turn, catalyzes the conversion of fibrinogen to fibrin, resulting in a stable fibrin matrix. Additionally, the platelet receptor glycoprotein (GP) IIb/IIIa binds with fibrinogen, resulting in further platelet aggregation and subsequent occlusive coronary thrombus. An understanding of the contribution of these substances to the development of thrombus has led to wide clinical investigation of fibrinolytic, antithrombin, and antiplatelet drugs as therapeutic agents in patients with acute ischemic syndromes.

All thrombolytic agents exert their effects by activating the enzyme plasminogen and converting it to plasmin. Plasmin is capable of digesting fibrinogen, a major component of clots. The 3 thrombolytic agents currently approved for intravenous use in acute MI are streptokinase, anisoylated plasminogen-streptokinase activator complex (anistreplase, or APSAC), and tissue plasminogen activator (t-PA).

Streptokinase: Streptokinase works by joining to plasminogen in a complex that converts neighboring plasminogen to plasmin, a proteolytic enzyme capable of lysing fibrin clots.[3] Streptokinase activates fibrin-bound and circulating plasminogen equally and thus lacks significant fibrin specificity. The breakdown of circulating fibrinogen into fibrin degradation products results in antiplatelet and anticoagulant effects as well as reducing serum viscosity.[4–7] Since streptokinase is a product of β-hemolytic streptococci, it is antigenic and may produce allergic reactions in patients with recent streptococcal infections. Allergic reactions consisting of pruritus, rash, or fevers occur in 5% of patients, are usually quite mild, and are easily treated with antihistamines or antipyretic agents.

The incidence of anaphylaxis is approximately 0.1%.[3] Although the pharmacologic half-life of streptokinase is 30 minutes, depletion of fibrinogen usually lasts for 24 hours.[8] Antibodies develop approximately 5 days after streptokinase therapy and persist for 6 months to 1 year; therefore, it is recommended that patients not be re-treated with streptokinase (or its derivative, APSAC) during that time interval. Hypotension, due to vasodilation, occurs in approximately 10–15% of patients given streptokinase. Patients who exhibit hypotension can be treated easily by temporarily stopping or decreasing the infusion rate of streptokinase and administering intravenous fluids.

The advantages of streptokinase, with or without the additive effect of aspirin,[9] include its proven track record in tens of thousands of patients, its cost savings at $100–300 per dose, and its ability to improve left ventricular function and save lives. Disadvantages of streptokinase include the potential for allergic reactions and hypotension (although some believe that afterload reduction is beneficial after an MI). Although coronary reperfusion occurs more slowly with streptokinase than with other available agents, this has not translated into worsened clinical outcome.

Tissue plasminogen activator: t-PA is a naturally occurring human protein that is nonantigenic and may be readministered immediately in the event of reinfarction.[3] Derived by recombinant DNA technology, t-PA is fibrin-specific. Therefore, t-PA selectively binds to the fibrin of clots and the resulting complex converts neighboring plasminogen to plasmin, producing more localized thrombolysis. Although this has resulted in lesser depletion of circulating fibrinogen, fibrin specificity has not resulted in a reduced incidence of bleeding complications.[8] Further, the short plasma half-life of t-PA (5 minutes) may result in a higher rate of infarct vessel reocclusion and has resulted in the widespread use of concomitant intravenous heparin. The dose of t-PA recommended by the Food and Drug Administration is 100 mg over 3 hours (60 mg, 20 mg, and 20 mg over hours 1, 2, and 3, respectively). Patients with a small body size have been shown to have an increased risk of bleeding complications with t-PA therapy. Therefore, in patients who weigh <65 kg, a total dose of 1.25

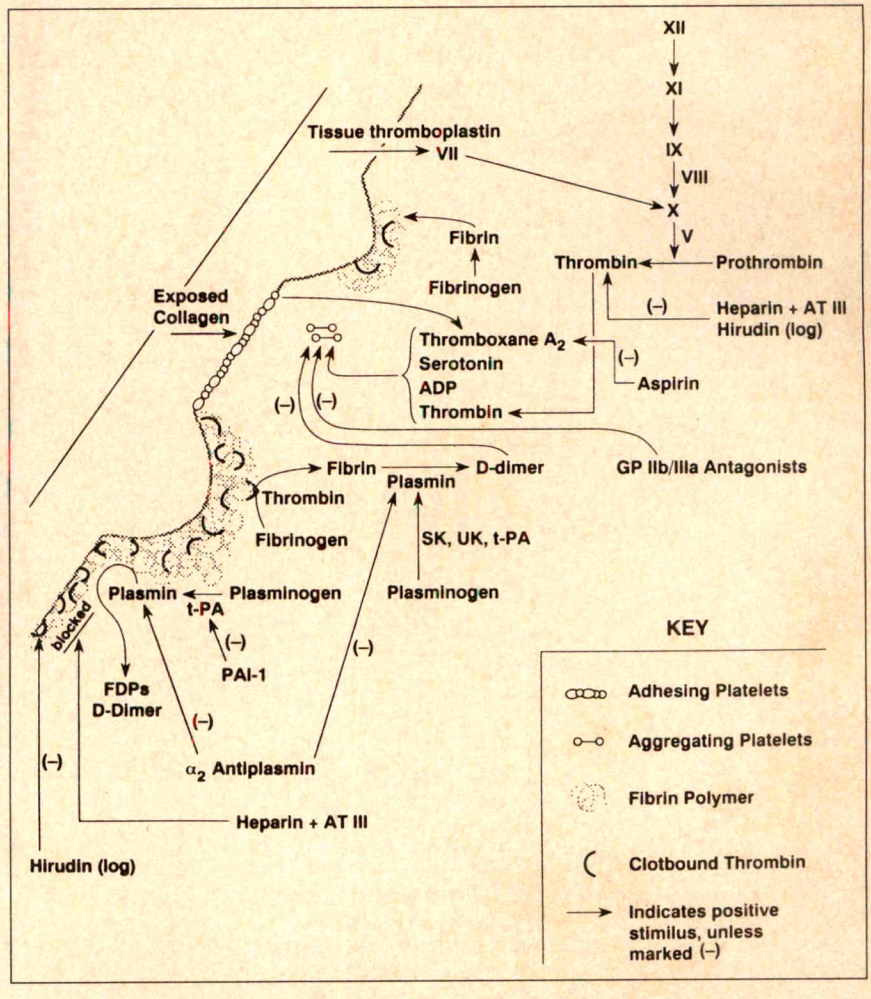


FIGURE 1. Platelet, thrombin, and arterial interactions that result in thrombosis and site of action of therapeutic agents. ADP = adenosine diphosphate; AT III = antithrombin III; FDPs = fibrin degradation products; GP = glycoprotein; PAI = plasminogen activator inhibitor; SK = streptokinase; t-PA = tissue plasminogen activator; UK = urokinase. (Reprinted with permission from *J Am Coll Cardiol.*[2])

mg/kg is administered over 3 hours with 10% as a bolus, 50% over the first hour, and 40% over the last 2 hours.

Advantages of t-PA include its lack of antigenicity, allergic reactions, and hypotension during infusion. Acute reperfusion rates have been demonstrated to be higher than that of streptokinase therapy.[10–14] Reocclusion may also be higher, however, and clinical endpoints of left ventricular function, long-term patency, and mortality have been quite similar between the 2 agents. Disadvantages of t-PA include the complicated dosing regimen, the need for concomitant heparin administration, a higher rate of stroke, and its cost, which is $2,300 for a single dose at our institution.

Anisoylated plasminogen streptokinase activator complex: APSAC is a new, second-generation thrombolytic agent that has been recently approved for intravenous use.[3] This drug was developed to overcome some of the limitations of intravenous streptokinase therapy. Temporary protection of the active enzymatic site of the plasminogen streptokinase complex by acylation allows APSAC to be given by rapid injection, thus improving bioavailability at the site of the clot and prolonging fibrinolytic action. This acylated derivative of streptokinase has several properties that differ from the parent compound, including greater fibrin binding and a longer duration of action (pharmacologic half-life of 90 minutes). These properties simplify intravenous administration and potentially improve coronary reperfusion and reduce reocclusion rates.

The currently approved 30 U dose has been demonstrated to result in acute infarct vessel patency rates of approximately 60–70%, improved ventricular function, and reduced mortality.[15,16] As with streptokinase, its effectiveness in acutely opening coronary arteries is reduced in the later hours of MI (>4 hours from chest pain onset), but 24-hour patency rates are similar to other available agents.

Advantages of APSAC include the ability to administer the entire dose as a bolus over 2–5 minutes, moderate expense, and the ability to open acutely more arteries than is possible with streptokinase therapy. The potential for allergic and hypotensive reactions remains, however, and this agent has not been demonstrated to be superior to streptokinase or t-PA with regard to improvement in ventricular function or reduction in mortality.

Clinical endpoints after thrombolytic therapy: In order to select a particular thrombolytic agent, it is important to compare the clinical benefits derived from various thrombolytic drugs. Clinical endpoints after thrombolytic therapy have included infarct vessel patency, left ventricular function, mortality, and complications, i.e., bleeding, reocclusion, or allergic reactions.

The first Thrombolysis in Myocardial Infarction (TIMI-1) trial, sponsored by the National Heart, Lung, and Blood Institute, provided some of the earliest data supporting the clinical efficacy of thrombolytic agents.[11] Patients with an occluded infarct vessel documented by pretreatment angiography were randomized to receive intravenous streptokinase or t-PA. In patients treated with streptokinase, 35% of occluded vessels were reperfused by 90 minutes, whereas a 60% reperfusion rate was observed with t-PA treatment. Since that time, t-PA has been consistently shown to be the fastest of the thrombolytic agents in terms of establishing patency. Streptokinase, which is not fibrin-specific, is slower in effect. APSAC, an agent with only mild fibrin specificity, results in a rate of opening somewhat faster than streptokinase. Streptokinase and APSAC have more gradual reperfusion, referred to as the catch-up phenomenon, and by 24 hours no difference in patency has been observed between t-PA and other agents[17] (Figure 2). Further, studies utilizing catheterization performed 1–3 weeks after treatment demonstrated maintenance of equivalent patency rates with the 3 agents over time.

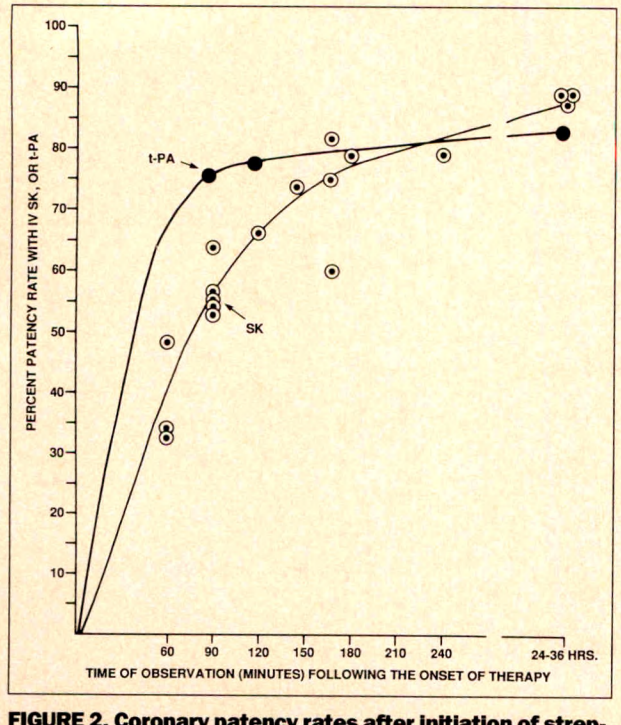


FIGURE 2. Coronary patency rates after initiation of streptokinase (SK) or tissue plasminogen activator (t-PA) from angiographic studies in which thrombolytics were initiated approximately 3 hours after symptom onset. (Reprinted with permission from *Ann Intern Med.*[17])

Before the thrombolytic era, it was well established that left ventricular function was an important predictor of prognosis after acute MI.[18] All thrombolytic drugs have been demonstrated to improve regional and global ventricular function when compared with placebo.[19] Small trials that directly compared streptokinase with t-PA showed that the 2 agents were similar in preserving left ventricular function.[20,21] The Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarcto Miocardico (GISSI-2) randomized 12,490 patients to receive either t-PA or streptokinase and found no difference in left ventricular function or incidence of congestive heart failure between the 2 groups.[22]

The most obvious clinical benefit of thrombolytic therapy is its lifesaving potential. The placebo-controlled trials have demonstrated that the use of streptokinase,[9,23–27] t-PA,[28] or APSAC[15] saves lives. Recently, direct comparisons incorporating nearly 70,000 patients demonstrated mortality to be virtually identical in patients treated with available thrombolytic agents. The GISSI-2[22] plus international extension[29] randomized 20,891 patients to receive t-PA versus streptokinase, with a second randomization to subcutaneous heparin 12,500 U twice daily started at hours 12, versus no heparin (Table I). There was no difference in mortality between t-PA- and streptokinase-treated patients (8.9 vs 8.5%, respectively; difference not significant). Major cardiac events, including reinfarction, congestive heart failure, and progression to cardiogenic shock, were similar between the t-PA- and the streptokinase-treated groups. As expected, hypotension and allergic reactions occurred more frequently after streptokinase therapy. Although t-PA was associated with a significantly higher incidence of stroke compared with streptokinase (1.3 vs 1.0%), this was attributed to an inadequate heparin regimen that may have resulted in more embolic strokes.

These results, however, were confirmed in the Third International Study on Infarct Survival (ISIS-3) trial.[30] This was a multicenter randomized, double-blind trial in which 41,299 patients were randomized to receive t-PA, streptokinase, or APSAC with a second randomization to subcutaneous heparin 12,500 U twice daily started at hour 4, or no heparin (Table I). There was no evidence of any difference in mortality among streptokinase (10.6%), t-PA (10.3%), and APSAC (10.5%), either overall or in the subgroup with ST-segment elevation randomized <6 hours from symptom onset. Disturbingly, t-PA was again associated with a higher incidence of stroke compared with streptokinase (1.4 vs 1.0%, $p < 0.01$), which appeared to be due to an increased rate of definite or probable cerebral hemorrhage (0.7 vs 0.2%, $p < 0.00001$).

TABLE I Mortality Trials Directly Comparing Thrombolytics

	International GISSI-2[22,29]		ISIS-3[30]		
	SK	t-PA	SK	t-PA	ASPAC
Mortality	8.5	8.9	10.6	10.3	10.5
Reinfarction	3.0	2.6	3.5	2.9*	3.6
Stroke	1.0	1.3*	1.0*	1.4	1.3
All bleeding	3.9	5.0	4.5	5.2	5.4
Transfusions	0.9	0.6*	0.9	0.8	1.0
Hypotension	4.4	2.0*	6.7	4.4*	7.0
Allergy	1.7	0.2*	3.6	0.8*	5.0

*$p < 0.05$
APSAC = anisoylated plasminogen streptokinase activator complex (anistreplase); SK = streptokinase; t-PA = tissue plasminogen activator.

It is not entirely clear why the high acute patency rates observed after t-PA have not resulted in greater preservation of ventricular function and improved mortality. It has been suggested that most patients are treated too late to have substantial limitation in infarct size, which may occur only if reperfusion occurs in the first 1–2 hours.[17] Later application of thrombolytic drugs may improve survival by later reperfusion with subsequent reduction in infarct expansion, aneurysm formation, and malignant arrhythmias.[31] In practice, thrombolytic therapy is given at an average of 4 hours after the onset of symptoms, which may explain why patency rates for the different thrombolytic agents fail to translate into differences in clinical outcome. Each of the thrombolytic agents currently available offers advantages in a particular clinical setting. Streptokinase offers the advantages of a deficit of intracranial hemorrhage and lower cost. APSAC can be administered rapidly as a bolus injection, minimizing delay of onset of therapeutic effect. Consequently, APSAC may be the preferred thrombolytic agent for prehospital administration, i.e., use by an emergency squad or at an urgent care center, with subsequent transfer. An advantage of t-PA is the lack of severe allergic reactions in patients previously treated with streptokinase or APSAC.

ANTIPLATELET DRUGS

Platelets are important in the initiation of thrombosis in acute MI, as well as the inability of thrombolytic agents to dissolve a clot, a phenomenon known as thrombolytic resistance.[32,33] Platelets are also important in reocclusion of an infarct vessel, reinfarction, and poor clinical outcome.[34] Platelets do not adhere to normal vascular endothelial cells. In areas of endothelial disruption, how-

TABLE II Pharmacology of Platelet-Inhibiting Agents

Agents that inhibit platelet adhesion
von Willebrand factor monoclonal antibodies
Aurintricarboxylic acid
Agents that inhibit platelet aggregation
Aspirin (other nonsteroidal antiinflammatory drugs)
GP IIb/IIIa receptor blockers
Monoclonal antibodies
RGD-containing peptides
Ticlopidine—inhibits exposure of GP IIb/IIIa
Thromboxane/endoperoxide receptor inhibitors
Dextran
Omega-3 fatty acids
Fibrin degradation products—systemic lytic agents
Agents that inhibit platelet activation
Dipyridamole
Prostaglandin E_1
Prostacylin
Calcium channel antagonists
Agents that inhibit platelet growth factors
Trapidil

Adapted with permission from *Cardiology*.[33]
GP = glycoprotein; RGD = Arg-Gly-Asp.

ever, they adhere to exposed collagen and other adhesive glycoproteins. Platelet adhesion (adherence to subendothelial surfaces) is mediated primarily by von Willebrand factor binding to the platelet receptor GP IIb. Platelet aggregation (clumping) is mediated by the linking of 2 platelets by fibrinogen bound to the platelet GP IIb/IIIa receptor. Platelets adhere and aggregate in response to several agonists, including thromboxane, adenosine diphosphate, collagen, thrombin, serotonin, epinephrine, and platelet-aggregating factor. As demonstrated in Figure 3, all agonists can initiate release of arachidonic acid, which increases production of thromboxane A_2 leading to exposure of the platelet GP IIb/IIIa receptor.[32] Significantly, all agonists can independently expose GP IIb/IIIa and platelet aggregation can occur even if the arachidonic acid pathway is completely blocked, i.e., with aspirin.

Several therapeutic strategies (Table II) aimed at inactivating platelets have focused on the pathways outlined in Figure 3. Despite many potential therapeutic agents, to date the only agent proven to be efficacious at preventing MI in humans is aspirin. Aspirin inhibits cyclooxygenase activity and thus thromboxane A_2 synthesis for the lifetime of the platelet. Adherence and platelet release of growth factors, however, are not affected by aspirin.[32,33] Three randomized, placebo-controlled clinical trials previously demonstrated that aspirin administered to patients with unstable angina reduces the incidence of progression to MI and death

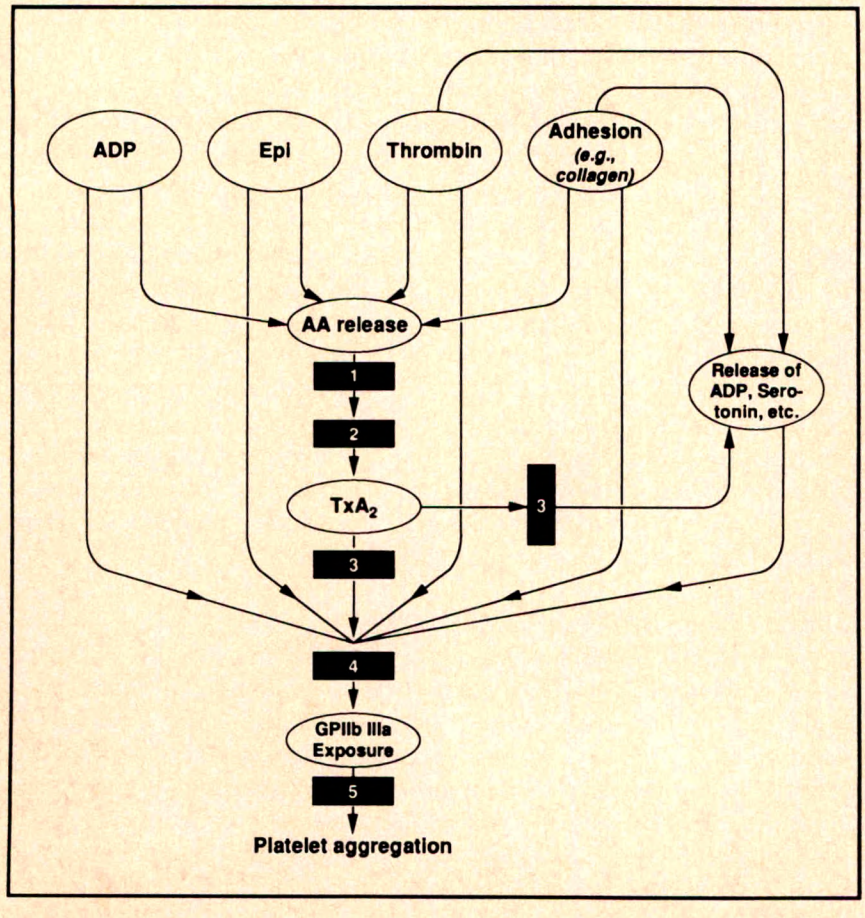


FIGURE 3. Platelet-activation mechanisms leading to platelet aggregation. Major agonists that aggregate platelets include adenosine diphosphate (ADP), epinephrine (Epi), and thrombin. In addition, platelet adhesion mediated by collagen or adhesive glycoproteins in the subendothelium is another potent stimulus for platelet activation. All these agonists can cause the release of arachidonic acid (AA), but even if the arachidonic acid pathway is blocked, they can expose glycoprotein (GP) IIb/IIIa receptors and cause platelet aggregation by other mechanisms. Antiplatelet agents are targeted at blocking different enzymes or receptors of the platelet activation sequence: (1) Cyclooxygenase; (2) thromboxane (Tx) synthetase; (3) thromboxane receptor; (4) platelet cyclic adenosine monophosphate; (5) glycoprotein IIb/IIIa receptor. (Modified with permission from *N Engl J Med*.[32])

by 50%.[35–37] The dose of aspirin used in the majority of human trials ranged from 324 mg/day to 324 mg four times daily. This benefit was recently confirmed in 800 patients using lower-dose aspirin (75 mg/day) in patients with unstable angina.[38] Thus, aspirin is clearly effective in preventing mortality and morbidity associated with progression of unstable angina to acute MI.[3] Since lower-dose aspirin (75 mg) may not effectively suppress thromboxane activity in the first few days,[39–42] generally a higher dose of aspirin is recommended (160–324 mg).

It is clear that aspirin is beneficial in long-term secondary prevention after MI[43] as well as primary prevention[44] in males >40 years old. Until recently, clinical data supporting the benefits of aspirin in acute MI were very limited.[45] The ISIS-2 trial enrolled 17,000 patients with suspected MI and randomized them to either placebo, aspirin alone, streptokinase alone, or streptokinase plus aspirin.[9] Aspirin was given within 24 hours of chest pain onset, administered as a 160 mg dose chewed immediately and continued for 4 weeks. When compared to placebo, the aspirin group had a decrease in mortality of 21% at 5 weeks (Table III). The combination of streptokinase and aspirin was associated with fewer reinfarctions (1.8 vs 2.9%), strokes (06. vs 1.1%), and deaths (8 vs 13.2%) compared with placebo. This difference remained significant after a median of 15 months' follow-up. Bleeding complications with aspirin were minimal in the ISIS-2 trial (Table IV).

Early administration of aspirin may be particularly important in conjunction with thrombolytic therapy due to an early procoagulant effect of thrombolytic agents.[46–50] All thrombolytic agents generate plasmin from its inactive precursor plasminogen. In addition to the fibrin-digesting properties of plasmin, it may also result in platelet activation. In vitro platelet studies and measures of plasma and urinary metabolites of thromboxane A_2 suggest that platelet aggregation is enhanced by thrombolytic agents.[49–51] The generation of fibrinopeptide A is also observed in response to thrombolytic drug administration and may indicate the generation of thrombin, a potent platelet activator. The importance of aspirin therapy in the prevention of reocclusion and recurrent ischemia after thrombolysis has been emphasized in a recent meta-analysis of 32 angiographic studies in patients with acute MI.[52,53] Aspirin was administered in 2,309 patients and withheld in 1,721 patients who received either t-PA or streptokinase.[52,53] Aspirin therapy was associated with a higher patency rate at 90 minutes (72 vs 63%, p = 0.05), a lower rate of recurrent angina (28 vs 45%, p <0.001), and a lower rate of reocclusion (11 vs 29%, p <0.001), regardless of whether streptokinase or t-PA was used (Table V).

TABLE III Clinical Benefit of Aspirin

	ISIS-2 (%)	Ten Previous Trials (%)
↓ Nonfatal stroke	36 ± 17	42 ± 11
↓ Nonfatal reinfarction	49 ± 9	31 ± 5
↓ Vascular death	21 ± 5	13 ± 5
Any vascular event	27 ± 4	25 ± 5

↓ = decreased.
Adapted from *Circulation*.[45]

TABLE IV Side Effects of Aspirin in the ISIS-2 Trial

	Aspirin (n = 8,379)(%)	Placebo (n = 8,379)(%)	p Value
Drug stopped	7.1	7.2	NS
Documented CNS bleeding	0.06	0.06	NS
Major bleeding (i.e., transfused)	0.4	0.4	NS
Minor bleeding (i.e., not transfused)	2.6	1.9	<0.002

Adapted from *Lancet*.[9]
CNS = central nervous system; NS = difference not significant.

TABLE V Effect of Aspirin on Coronary Patency and Ischemia After Thrombolytic Therapy: A Meta-Analysis of 32 Studies

	Aspirin (%)	No Aspirin (%)	p Value
90-minute patency	72	63	0.05
In-hospital angina	28	45	0.001
Reocclusion after SK	11	25	0.01
Reocclusion after t-PA	10	26	0.01

Adapted from *J Am Coll Cardiol*.[52]
SK = streptokinase; t-PA tissue plasminogen activator.

The ability of thrombolytic agents to increase platelet activation may cause problems with intermittent patency and reocclusion of the infarct vessel. In time, however, depletion of serum fibrinogen and formation of fibrin degradation products occur with the nonfibrin selective agents streptokinase or APSAC.[3] Fibrin degradation products bind to platelet receptors and interfere with the binding of fibrinogen to platelets, lowering the risk of rethrombosis.[4–6] This may account for the findings of Foltz et al[54] regarding reduced platelet thrombus formation in stenosed animal coronary arteries after streptokinase. The short plasma half-life of t-PA and lack of fibrinogen depletion may predispose to early reocclusion and reinfarction. In a group of patients, all of whom received t-PA, less depletion of fibrinogen was observed in patients experiencing reocclusion compared with patients whose arteries remained patent.[55] Combined ad-

ministration of t-PA with a nonspecific thrombolytic agent might alleviate this problem. Studies utilizing combinations of t-PA with urokinase or streptokinase have reported a lower rate of reocclusion and recurrent ischemia. In the Fifth Thrombolysis and Angioplasty in Acute Myocardial Infarction (TAMI-5) study, reocclusion was 12% after monotherapy compared with 2% after t-PA/urokinase, $p = 0.04$.[56] We demonstrated that a less expensive regimen of half-dose t-PA combined with streptokinase resulted in reocclusion in only 3% of patients, compared with 10% after t-PA monotherapy ($p = 0.06$).[57] Since reocclusion is associated with a doubling of mortality,[58] a combination regimen that sustains arterial patency may be an advantage.

ANTITHROMBOTIC AGENTS

Fuster and Chesebro[59] have reviewed previous trials of antithrombotic therapy during acute MI. Their meta-analysis of 6 randomized trials found that the in-hospital use of anticoagulants reduced early mortality and reinfarction when compared with placebo. Since that time, the Studio sulla Calciparina nell'Angina e nella Trombosi Ventricolare nell'Infarcto (SCATI) trial randomized 711 patients with acute MI to receive high-dose subcutaneous heparin or no heparin, regardless of whether they received thrombolytic therapy.[60] In patients who received streptokinase, transient ischemic episodes were reduced in the heparin group (14.2%) compared with patients not receiving heparin (19.6%). The International t-PA/Streptokinase Mortality Trial and its constituent Italian GISSI-2 study randomized 20,000 patients to receive either t-PA or streptokinase with a second randomization to heparin (12,500 U subcutaneously twice daily starting 12 hours after thrombolytic therapy) or no heparin therapy.[22,29] Streptokinase and t-PA appeared to be equally effective in preventing in-hospital death. Heparin had no effect on survival, incidence of stroke, or other clinical events, but did result in a slight increase in the incidence of major bleeding complications.

The ISIS-3 trial treated patients with aspirin and thrombolytics (either streptokinase, t-PA, or APSAC) and randomized half to receive subcutaneous heparin (12,500 U twice daily for 7 days, starting 4 hours after thrombolytics were initiated).[30] During the scheduled heparin treatment (days 0 to 7), there were slightly fewer deaths in the heparin group than in the no heparin group (7.4 vs 7.9%, $p = 0.06$). Between days 7 and 35, however, there was a slightly greater mortality after discontinuation of heparin (3.1% of survivors) compared with the group that did not receive heparin (2.9%). Thus, the mortality rate at day 35 was similar in both groups (10.3 vs 10.6%). The heparin group tended to have fewer reinfarctions (3.16 vs 3.47%, $p = 0.09$). There was an increase in cerebral hemorrhage (0.56 vs 0.40%, $p < 0.05$), however, and other major bleeding (1.0 vs 0.8%, $p < 0.01$). These data suggest that the early benefit of heparin occurs with an accompanying increased risk of bleeding, and some of the early benefit may be lost after heparin ceases.

The findings of the GISSI-2 and ISIS-3 trials have generated considerable controversy because of the use of subcutaneous heparin rather than intravenous heparin.[61–63] In a study comparing the effects of t-PA with and without a bolus of intravenous heparin, patency rates after 90 minutes were similar with the 2 regimens.[62] Two studies in which no aspirin or a low dose of aspirin (80 mg) was administered, however, demonstrated an improved patency rate at 18–48 hours with adjunctive intravenous heparin compared with no heparin.[64,65] In a recent trial by the European Cooperative Study Group, patients treated with intravenous t-PA, then oral aspirin, were randomized to receive either heparin or no heparin.[66] The difference in patency rate in the 2 groups was narrowed by the addition of aspirin. In fact, a high patency rate was observed with t-PA and aspirin alone, suggesting that aspirin may be more important than heparin in preventing reocclusion.

In a preliminary report by O'Connor et al,[67] 250 patients who received APSAC were randomized to receive either intravenous heparin or no heparin. An angiogram on day 5 revealed no difference in coronary patency between the 2 groups, whereas bleeding complications were 2 times higher in heparin-treated patients. In the Antithrombotics in the Prevention of Reocclusion in Coronary Thrombolysis trial, patients with acute MI were treated with intravenous heparin and streptokinase.[68] After 48 hours, 300 patients in whom an open infarct vessel was demonstrated by cardiac catheterization were randomized to receive either placebo, aspirin, or warfarin (with continued intravenous heparin until a therapeutic effect, i.e., a prothrombin time twice that of control, was observed). A recatheterization performed 3 months later revealed a 30% rate of reocclusion despite these preventive measures. Aspirin administration was associated with a greater improvement in ejection fraction and reduction in recurrent ischemic events compared with placebo or warfarin.

Thus, antiplatelet agents may be more valuable than heparin or warfarin alone; however, their combined use will require further investigation.

To address these issues and to determine whether new lytic regimens designed to maximize patency will further reduce mortality, a large international thrombolytic mortality trial entitled Global Utilization of Streptokinase and t-PA for Occluded Coronary Arteries (GUSTO) has been initiated.[69] The GUSTO trial includes patients of any age who present <6 hours after chest pain onset with ST-segment elevation in ≥2 electrocardiographic leads. Aspirin 160 mg will be given to all patients, as will intravenous β blockers if no contraindications exist. Patients will be randomized to 1 of 4 thrombolytic strategies: intravenous heparin plus front-loaded t-PA, intravenous heparin plus combination t-PA/streptokinase, intravenous heparin plus streptokinase, or subcutaneous heparin plus streptokinase. To determine rates of infarct vessel patency and reocclusion, an angiographic substudy involving 2,400 patients will be conducted. Patients will be randomly assigned to 4 groups: no early catheterization, catheterization at 90 minutes, catheterization at 3 hours, or catheterization at 24 hours. All patients in this substudy will undergo catheterization at 7 days. The target enrollment for the overall study will be 40,000 patients to determine an absolute mortality difference of 1% between treatment groups. It is anticipated that the trial will be completed in late 1993.

Thus, early administration of heparin appears to be important in maintaining patency after t-PA infusion, particularly if an insufficient dose of aspirin is utilized. After APSAC therapy, early intravenous heparin administration does not appear to affect patency, and it increases the incidence of bleeding complications. Although the international trials found subcutaneous heparin was associated with a trend toward improved early survival, this slight benefit was not continued after hospital discharge.

CONCLUSION

All thrombolytic agents reduce mortality and improve left ventricular function to a similar degree. A slightly greater risk of stroke has been demonstrated with more fibrin-specific agents. The choice of a thrombolytic agent should be based on practical considerations, including the familiarity of the physician with a particular agent, ease of administration, previous allergic reactions to thrombolytic therapy, and cost. Aspirin in doses of at least 160–324 mg should be administered acutely, since this is well documented to decrease mortality, reinfarction, and stroke. Heparin is usually administered during the hospital stay. The precise dose, timing, and route of administration, however, have not been determined in a prospective randomized trial.

Acknowledgment: The author gratefully acknowledges Margaret Schmidt for manuscript preparation.

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Cholesterol-Lowering Drugs as Cardioprotective Agents

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A detailed overview of the various forms of hyperlipidemia/dyslipidemia that constitute a major risk factor for coronary heart disease and a detailed discussion of the various types of cholesterol-lowering drugs are presented. The importance of identifying the type of dyslipidemia with respect to the choice of treatment is emphasized, as is the use of nonpharmacologic intervention, i.e., diet, exercise, and weight loss. The appropriate use and benefits of bile acid sequestrants, nicotinic acid, fibric acids, 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, and probucol are individually discussed, whereas nonpharmacologic approaches used in conjunction with the drugs are recommended emphatically.

(Am J Cardiol 1992;70:27 I–32 I)

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High serum cholesterol is a major risk factor for coronary artery disease (CAD).[1] For most hypercholesterolemic patients, an increase in serum total cholesterol indicates an elevation of low-density lipoprotein (LDL), the major atherogenic lipoprotein. Other forms of dyslipidemia, however, notably an increase in very-low-density lipoprotein (VLDL) or a decrease in high-density lipoprotein (HDL), likewise increase the risk for CAD. Approximately one third of CAD in the United States can be explained by dyslipidemia in the general population. The other two thirds are about equally divided between the other 2 major risk factors: hypertension and cigarette smoking. Most of the dyslipidemia in the United States is the result of the dietary excesses of the typical American diet, but in a substantial minority of people, genetic abnormalities in the metabolism of lipoproteins are important as well. In some of the latter, drug therapy, in addition to dietary modification, may be required for the correction of dyslipidemia. In the following discussion, the term "dyslipidemia" will be used in preference to "hyperlipidemia" because it will include conditions in which low HDL-cholesterol levels are present.

There are 3 major causes of dyslipidemia. One cause includes dietary excesses (dietary saturated fatty acids and cholesterol and excess intake of total calories leading to obesity). Another includes the genetic forms of hyperlipidemia (e.g., familial hypercholesterolemia, familial hypertriglyceridemia, and familial combined hyperlipidemia). These genetic disorders can occur either on a monogenic or polygenic basis. The term "mixed hyperlipidemia" will refer to increases in both serum total cholesterol and triglycerides. Finally, dyslipidemia often is secondary to other conditions, such as diabetes mellitus, hypothyroidism, renal disease, or drugs (e.g., β-adrenergic blocking agents). Common causes of low HDL-cholesterol level are obesity, cigarette smoking, lack of exercise, β-adrenergic blocking agents, androgenic steroids, and hypertriglyceridemia.

When evaluating a patient with dyslipidemia, it

is important to rule out the secondary causes. Many patients have abnormalities in plasma lipoproteins because of other diseases, especially diabetes mellitus and renal disease. Various drugs likewise can cause dyslipidemia; for example, β-adrenergic blocking agents can induce severe hypertriglyceridemia in a patient who otherwise would have only mildly elevated triglycerides. All patients with hypercholesterolemia should undergo testing for hypothyroidism; some hyperlipidemic patients prove to be deficient in thyroid hormone in the absence of clinical signs.

Dietary excesses are another important cause of dyslipidemia. High levels of LDL-cholesterol commonly are the result of excess intake of saturated fatty acids and cholesterol, and levels can be further accentuated by obesity. Effective therapy requires elimination of these factors, and, in many cases, this is all that is needed for a normalization of cholesterol levels. Hypertriglyceridemia can be induced by obesity or excess intake of alcohol; thus, weight reduction and decreased alcohol intake are required for patients with elevated triglycerides. In a patient with isolated low HDL-cholesterol (i.e., without concomitant hyperlipidemia), HDL levels may be raised by weight reduction, if the patient is obese, or by increased exercise. Hygienic therapy is the first line of treatment for dyslipidemia in general, and dietary therapy still should be employed, even if the patient has a genetic dyslipidemia and even if drug treatment is needed. Control of obesity is especially important because it has many beneficial effects: weight reduction will lower cholesterol and triglyceride levels, raise HDL-cholesterol levels, and often reduce blood pressure.

Cholesterol-lowering drug therapy should not be instituted until the existence of definite dyslipidemia has been established, the form of dyslipidemia identified, secondary causes excluded, and response to diet defined. Many patients are started on drugs without adequate evaluation, and, since drug therapy presumably will be lifelong, this approach cannot be justified. A single measurement of plasma lipids is inadequate; multiple measurements are preferable. Drug therapy should be considered only after the presence of distinct dyslipidemia has been confirmed and inadequate response to diet has been demonstrated. In general, a 6-month trial of dietary therapy is prudent. The decision to use drug therapy also should depend on the risk status of the patient. For example, patients with established CAD should be treated more vigorously at lower lipid levels than those without CAD. In addition, patients who have multiple risk factors (e.g., smoking, hypertension, and diabetes) deserve drug therapy before those without other risk factors.

Agents currently available for lowering serum cholesterol levels include the bile acid sequestrants, nicotinic acid, inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, the fibric acids, and probucol. Two bile acid sequestrants—cholestyramine and colestipol—are available. The available HMG-CoA reductase inhibitors include lovastatin, pravastatin, and simvastatin. Two fibric acids—clofibrate and gemfibrozil—can be prescribed in the United States, and 2 others—fenofibrate and bezafibrate—are widely used in other countries. The drugs all differ in their mechanisms of action, potency, and safety. Therefore, a knowledge of their efficacy and safety profiles is necessary if they are to be used appropriately.

BILE ACID SEQUESTRANTS

The primary action of the bile acid sequestrants is to remove bile acids from the intestinal tract, thereby interrupting their enterohepatic circulation. Normally, the resorption and return of bile acids to the liver inhibit the conversion of cholesterol to bile acids. When bile acids are removed from the enterohepatic circulation, the transformation of cholesterol into bile acids in the liver is increased, and this lowers hepatic cholesterol concentrations. As a result, the synthesis of receptors for LDL is increased, which causes a decrease in circulating LDL levels. Depending on the dose used and individual responsiveness, bile acid sequestrants lower the LDL-cholesterol level by 15–25%.

Cholestyramine, a bile acid sequestrant, was used as the active drug in the Lipid Research Clinic Coronary Primary Prevention Trial (LRC-CPPT).[2,3] In this study, approximately 4,000 patients were treated with either active drug or placebo for 7 years. Cholestyramine lowered total cholesterol on an average of about 11%, and this effect resulted in a 19% reduction in rates of CAD, compared with placebo. Patients who adhered completely to the prescribed dose had even greater reductions in cholesterol levels, and subgroup analysis revealed that they had a greater reduction in CAD risk. Thus, the LRC-CPPT demonstrated that lowering cholesterol levels by drug therapy will significantly decrease the risk for CAD. The degree of reduction in risk was similar to that projected from epidemiologic studies; namely, for every 1% reduc-

tion in cholesterol levels, the risk for CAD was reduced by 2%.

In the LRC-CPPT,[2,3] a dose of cholestyramine of 16–24 g/day was prescribed. Many patients, however, could not tolerate such high doses. There is growing evidence that lower doses (e.g., 8 g/day cholestyramine or 10 g/day colestipol) will produce a 10–15% reduction in total cholesterol levels in many patients. This response should reduce risk for CAD by about 20–30%. If low doses of bile acid sequestrants are combined with dietary therapy, which should reduce cholesterol levels by about 10%, the net reduction of CAD risk should be approximately 40–50%. Thus, the combination of diet and low-dose bile acid sequestrants should be sufficient therapy for many patients with moderate hypercholesterolemia. Since the majority of patients with elevated serum cholesterol levels have only moderate hypercholesterolemia (i.e., total cholesterol in the range of 240–275 mg/dL), dietary therapy plus low-dose bile acid sequestrants should provide sufficient therapy for most patients with elevated LDL-cholesterol levels.

NICOTINIC ACID

The major action of nicotinic acid appears to be inhibition of the production of VLDL. This, in turn, lowers levels of both VLDL and LDL. Nicotinic acid also increases HDL levels, possibly by its action to lower VLDL levels. In many patients, however, the increase in HDL levels exceeds that which would be expected from the decrease in VLDL–triglyceride levels. Overall, the effects of nicotinic acid are very favorable. Moreover, the drug has proven to be effective in reducing the risk for CAD. For example, in the Coronary Drug Project,[4] a secondary prevention trial, nicotinic acid therapy reduced the number of second myocardial infarctions. The drug also has been used in combined drug therapy in other secondary prevention trials, and again beneficial effects have been observed. Therefore, it would appear that nicotinic acid has the potential to retard the development of coronary atherosclerosis.

The lipoprotein response to nicotinic acid appears to be proportional to the dose. Because of side effects, it is necessary to start the drug at low doses (e.g., 100 mg 3 times daily) with a gradual increase. Dose levels are 500, 1,000, and 1,500 mg 3 times per day. The highest dose produces the best results, but, because of side effects, a lower dose may be all that is tolerated. Nicotinic acid can be given in crystalline form and sustained-release form. The former produces more subjective side effects, and the sustained-release form usually is better tolerated. Unfortunately, sustained-release nicotinic acid appears to be more likely to induce hepatotoxicity. For this reason, crystalline nicotinic acid is preferable if it can be tolerated.

The usefulness of nicotinic acid is limited by the relative frequent occurrence of side effects. These include skin problems—flushing, itching, and skin rash—gastrointestinal distress, hepatotoxicity, a worsening of glucose tolerance in some patients, hyperuricemia, and lassitude and fatigue, the latter 2 possibly related to mild hepatotoxicity. About 50–67% of the patients started on nicotinic acid can tolerate it for long periods.

HMG-CoA REDUCTASE INHIBITORS

This class of drugs inhibits the synthesis of cholesterol in the liver.[5] Reduced hepatic concentrations of cholesterol stimulate the synthesis of LDL receptors, which promotes the clearance of LDL and VLDL remnants. This, in turn, leads to a reduction of levels of LDL-cholesterol and VLDL-cholesterol. Triglyceride levels also fall modestly. Although these drugs are expensive, they are highly effective in lowering cholesterol levels. Doses of 20 mg/day of lovastatin and pravastatin (or 10 mg/day of simvastatin) generally will lower LDL-cholesterol levels by about 25%. Clinically significant toxicity occurs in $<1\%$ of patients and is dose related. Rare patients will show increases in transaminases, suggestive of hepatotoxicity. Others can have muscle weakness and pain and elevations of creatine kinase, indicative of myopathy. If myopathy is severe, the patient may develop myoglobinuria and even acute tubular necrosis. Fortunately, myoglobinuria is rare and is usually the result of HMG-CoA reductase inhibitors used with other drugs, e.g., fibric acids or cyclosporine. Some patients have gastrointestinal symptoms, especially diarrhea, and an occasional patient may complain of insomnia. Adverse effects are readily reversed by stopping the drug, or, in many cases, by reducing the dose.

FIBRIC ACIDS

The primary action of the fibric acids is to increase the activity of lipoprotein lipase; hence, they are mainly triglyceride-lowering drugs.[6] Through this mechanism, they cause a modest increase in HDL-cholesterol levels. Lowering of triglycerides likewise can be accompanied by an increase in LDL-cholesterol levels, which may be a drawback of this class of drugs. On the other hand, if the patients do not have high triglycerides, the

fibric acids may lower LDL-cholesterol levels by 5–15%.

The World Health Organization trial[7] examined the effects of clofibrate in primary prevention of CAD. Patients with hypercholesterolemia were randomized into treatment and placebo groups. Those receiving the active drug had a significant reduction in the new onset CAD. Total mortality, however, was not reduced; in fact, total mortality actually may have been increased. Thus, the conclusion was drawn that clofibrate may be a toxic drug in which the side effects outweigh the benefits. This trial resulted in a decline in the use of clofibrate. The precise reason for the observed increased mortality during clofibrate therapy has never been determined. This drug, like other fibric acids, has side effects, some of which are potentially dangerous. One side effect is cholesterol gallstones, and it is possible that complications from gallstones could increase mortality. Other side effects are myopathy, leukopenia, and skin rash, but none of these have proven fatal. Therefore, it remains to be conclusively determined that fibric acids are inherently dangerous. The apparent increase in total mortality of the World Health Organization study may have been spurious.

The Helsinki Heart Study[8] evaluated the effectiveness of another fibric acid, gemfibrozil, for primary prevention of CAD. In this placebo-controlled trial, long-term, gemfibrozil therapy in men with hypercholesterolemia or mixed hyperlipidemia resulted in a progressive reduction in the incidence of coronary events over a 5-year period. In patients with hypercholesterolemia alone, a slight, nonstatistically significant reduction in CAD events was observed. In patients with elevations in both cholesterol and triglycerides, the decrease in the incidence of CAD was more dramatic. A subsequent analysis of effects in the various subcategories of patients in this trial revealed that gemfibrozil therapy produced a statistically significant reduction in coronary events only in patients with high triglycerides. Perhaps this is not surprising, since the major action of fibric acids is to lower the triglyceride level.

The treatment of patients with hypertriglyceridemia is controversial. For many years, elevated triglycerides were considered a less important risk factor for CAD than high cholesterol. More recently, however, secondary effects of triglyceride elevations have been implicated in atherogenesis and possibly thrombogenesis. It is now apparent that high serum triglycerides are accompanied by increases in postprandial lipoproteins (e.g., chylomicron remnants) and VLDL remnants; both types of lipoproteins probably are atherogenic. In addition, high triglycerides lower HDL-cholesterol levels and lead to the presence of small, dense LDL; both of these changes may be atherogenic. Finally, there is increasing evidence that high triglycerides promote thrombogenesis. Thus, elevated triglycerides may represent a definite mechanism for the development of CAD. If so, it would be reasonable to treat elevated triglyceride levels with fibric acids. Still, they probably should be used cautiously in primary prevention, since there has never been a primary prevention trial in hypertriglyceridemic patients to demonstrate efficacy of therapy.

Nevertheless, the combination of 2 triglyceride-lowering drugs—clofibrate and nicotinic acid—was tested on ischemic heart disease mortality in the Stockholm Ischemic Heart Disease Study.[9] In patients with established heart disease receiving these agents, mortality from ischemic heart disease was 36% lower than in the placebo group. Benefits on mortality were observed mainly in patients with hypertriglyceridemia and were proportional to the degree of reduction in triglyceride levels. It is not known whether the reduction in CAD mortality in this trial was the result of reduced atherogenesis, by modifying dyslipidemia, or inhibition of thrombogenesis.

PROBUCOL

Probucol is another drug with potential usefulness for prevention of coronary atherosclerosis. It mildly lowers LDL by promoting LDL clearance through the liver. The mechanism for increased LDL clearance is not known. Whether its cholesterol-lowering action has a beneficial effect on coronary atherogenesis is not known. It has another property, however, that may be more important than its effects on cholesterol levels. Probucol is an antioxidant, and it is carried in the LDL particle. Recent investigation suggests that oxidation of LDL within the arterial wall is a critical step in the uptake of LDL into macrophages to produce foam cells.[10] If this oxidation step could be prevented, then atherogenesis might be retarded. Probucol's antioxidant properties make it a candidate for this purpose. Indeed, studies in hypercholesterolemic animals have shown that probucol will prevent the development of atherosclerosis.[11] Whether it will exhibit the same property in humans remains to be determined.

If in fact antioxidants retard atherogenesis, whether certain vitamins (e.g., vitamin E, vitamin C, and β-carotene) act in the same way as probucol

can be questioned. Recent studies have shown that vitamin E will retard the oxidation of LDL in vivo,[12] and investigations in our laboratory indicate that vitamin C[13] and β-carotene[14] will interfere with LDL oxidation in vitro systems. Of course, it is not possible to recommend use of these vitamins for prevention of atherosclerosis without evidence of benefit from a clinical trial. Interruption of atherogenesis at the arterial wall level becomes an exciting possibility for research. Therapy directed at the arterial wall could be combined with serum cholesterol-lowering therapy to enhance retardation of atherogenesis.

DRUG TREATMENT OF SPECIFIC DYSLIPIDEMIAS

Familial hypercholesterolemia: This disorder is characterized by a genetic deficiency of LDL receptors. It occurs in 1 in 500 people and almost always in the heterozygous form. LDL-cholesterol levels usually are twice normal, and patients are prone to premature CAD. These patients deserve aggressive therapy of their hypercholesterolemia. The most effective therapy is the combination of HMG-CoA reductase inhibitors and bile acid sequestrants. With these agents, it usually is possible to reduce LDL-cholesterol concentrations to near normal.

Multifactorial hypercholesterolemia: About 20% of the adult population has cholesterol levels >240 mg/dL and is at increased risk for CAD. Their "hypercholesterolemia" usually is multifactorial in origin. Three factors—diet, aging, and genetics—combine to raise cholesterol levels to high levels in this group. Dietary modification is the first line of treatment; but if cholesterol levels are unusually high or if other CAD risk factors are present, drug therapy can be considered. Bile acid sequestrants are the drugs of first choice if there is an isolated increase in LDL cholesterol. HMG-CoA reductase inhibitors are more potent and better tolerated, although their long-term efficacy and safety have not been demonstrated.

Mixed hyperlipidemia: When levels of cholesterol and triglycerides are simultaneously increased, 3 factors often contribute: genetic factors, dietary excesses (saturated fatty acids, cholesterol, and obesity), and secondary causes (e.g., diabetes mellitus). Control of the latter 2 may lessen hyperlipidemia, but drug therapy may also be required. Several regimens of drug therapy can be employed. The first choice usually is nicotinic acid alone, since this drug will lower both triglyceride and cholesterol levels. Fibric acids alone are not effective: when they lower triglycerides, they may raise LDL-cholesterol levels. HMG-CoA reductase inhibitors are highly effective for lowering cholesterol levels and may cause moderate reductions in triglyceride concentrations; thus, they are an alternative to nicotinic acid. A highly efficacious regimen is to combine an HMG-CoA reductase inhibitor with a fibric acid; this combination will lower both cholesterol and triglycerides, and it also will raise HDL-cholesterol. Unfortunately, it is associated with increased risk for severe myopathy and must be used cautiously; the patient must be well-informed of this potential side effect, and if muscle soreness or weakness develops or if myoglobinuria occurs, the drugs must be stopped immediately.

Primary hypertriglyceridemia: A moderate elevation of triglycerides (250–500 mg/dL) in the presence of a low total cholesterol may not require drug therapy. There is controversy about whether levels in this range impart increased risk for CAD. If the patient has established CAD or if other CAD risk factors are present, however, treatment with nicotinic acid can be justified. A second choice is a fibric acid, but again it must be emphasized that a clinical trial to demonstrate the efficacy of drug therapy in patients with primary hypertriglyceridemia has never been carried out.

Isolated low HDL-cholesterol: Some patients have low HDL-cholesterol levels (<35 mg/dL) in the absence of other serum lipid abnormalities. Such patients certainly deserve hygienic therapy (weight reduction, smoking cessation, and increased exercise) in an attempt to increase HDL levels. If the patients are otherwise at low risk for CAD, drug therapy probably is not indicated; however, if CAD is already present, drug therapy may be warranted. Two approaches can be used: first, nicotinic acid can be used to increase HDL-cholesterol levels, or, second, an HMG-CoA reductase inhibitor can be used to produce a maximal reduction in LDL-cholesterol levels, so as to reduce the overall risk.

Dyslipidemia in patients with established CAD: Growing evidence indicates that aggressive lowering of serum cholesterol in patients with evident CAD will reduce subsequent CAD morbidity (i.e., additional nonfatal and fatal myocardial infarctions). Limited data further suggest that some coronary lesions may actually be reduced in size. Since patients with established CAD are at very high risk for subsequent cardiac events, cholesterol-lowering drug therapy can be justified to produce a maximal reduction in LDL-cholesterol levels. According to many investigators, it is reason-

able to lower the LDL-cholesterol level to <100 mg/dL in patients with established CAD. To do so will require cholesterol-lowering medications in many patients.

CONCLUSION

In the future, the use of cholesterol-lowering drugs for cardioprotection is likely to be expanded greatly. Data are accumulating to show benefit for cholesterol lowering, particularly in patients with established CAD or who are otherwise at high risk for CAD. The introduction of HMG-CoA reductase inhibitors has already considerably expanded the use of lipid-lowering therapy, and this trend is likely to accelerate in the future. New and more effective agents probably will be developed in the next few years. Thus, the addition of lipid-lowering drugs to the pharmacologic armamentarium will be a major step in the promotion of cardioprotection, particularly in high-risk patients or those with existing CAD.

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A View From Europe

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The pharmacologic approach to coronary protection, defined here as the prevention or delay of sudden death and myocardial infarction (without negatively affecting noncardiac mortality), is critically discussed. The value of pharmacologically treating mild hypertension and mild hypercholesterolemia is questioned, and the need for well-designed, randomized clinical trials with definitive endpoints to determine a drug's cardioprotective capability is emphasized. Based on such studies, it is concluded that some (but perhaps not all) β-receptor antagonists as well as aspirin have been shown to protect against sudden cardiac death. Trials of thiazide diuretics, calcium antagonists, and angiotensin-converting enzyme inhibitors have not shown a reduction in sudden cardiac death, despite having individual benefits with respect to other aspects of cardiovascular disease. The demonstration that some β blockers are cardioprotective is discussed in terms of the pathophysiology of sudden cardiac death, and differences in the pharmacokinetic profiles of individual agents.

(Am J Cardiol 1992;70:33 I–39 I)

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Coronary protection can be defined as the prevention or delay of sudden cardiac death and myocardial infarction (MI), without negatively affecting noncardiovascular mortality. The aggressive pharmacologic approach to coronary protection as practiced in the United States contrasts with the more conservative approach taken in Europe[1]—e.g., the aggressive approach to treating hypercholesterolemia taken in the United States, despite little evidence supporting a role for drug therapy in mild hypercholesterolemia.[1–3] More extensive study and perhaps new drugs are necessary to demonstrate a reduction in risk with cholesterol-lowering agents in patients with mild hypercholesterolemia, because present data may indicate a negative effect on noncardiovascular mortality with cholesterol-lowering drugs.[2,3] Another problem is also the lack of methods able to measure cholesterol accurately. With current techniques, a single sample can vary by 30% over a 2-week period.[4] Further, the cost of controlling hypercholesterolemia is an important consideration. Cholesterol-lowering drugs are expensive, and the cost-effectiveness of reducing cholesterol on a broad scale is an important issue in the United States and in Europe.

CORONARY PROTECTION—U.S. AGGRESSIVENESS AND EUROPEAN RESERVATIONS

In common with their more conservative view toward the treatment of mild hypercholesterolemia, European experts in the hypertensive field have expressed disagreements with the position of experts in the United States on the use of antihypertensive drugs in patients with mild hypertension.[1] For example, the British view toward the treatment of mild hypertension was highlighted in a report of the British Hypertension Society Working Party.[5] The criteria in this document are considerably more cautious than those advocated in the fourth Joint National Committee report from the United States.[6] The impression is that U.S. colleagues sometimes are too aggressive with regard to drug treatment of mild hypertension as well as of mild hypercholesterolemia. On what evidence, then,

TABLE I Coronary Protection—Present Evidence From Secondary or Primary Preventive Studies

Positive effect of:	
Smoking cessation	Some β blockers
Dietary changes	Aspirin

should medical professionals base treatment decisions and make the best choice among treatment alternatives? This is not an easy question to answer, but the aim of this article is to comment briefly on this issue and to summarize the data available, especially with regard to antihypertensive treatment. More comprehensive reviews are presented elsewhere.[7,8]

IMPORTANCE OF RANDOMIZED CLINICAL TRIALS AND TOTAL MORTALITY

Preventive measures are sometimes based solely on the identification and treatment of so-called risk factors. The risk-factor approach to coronary protection is, however, associated with several problems, since the experience from randomized clinical trials illustrates that affecting a coronary risk factor in a favorable way does not necessarily correspond to reduction in risk for coronary events or total mortality. Examples of this are the effect of antihypertensive thiazide diuretic therapy on coronary artery disease (CAD) in middle-aged men[7–9] and the effect of cholesterol-lowering drugs on noncardiovascular mortality.[2,3] Thus, an intervention may be effective in affecting a risk factor but may be harmful in other respects.

This may be exemplified further with results from the International Nifedipine Trial on Atherosclerotic Therapy in which active pharmacologic treatment (nifedipine) reduced the risk for new coronary lesions but significantly increased the risk for total mortality and sudden death, and with the results from the Cardiac Arrhythmia Suppression Trial in which antiarrhythmic drugs (encainide or flecainide) gave an impressive decrease in complex arrhythmias but increased total mortality because of an increase in sudden death.[10–12] Thus, simply identifying and treating a risk factor is not satisfactory. The clinical trial, however, is a key research activity with the potential to improve the quality of health care by careful comparison of alternative treatments.[13] In these trials, total mortality should be considered, as well as cause-specific fatal events in addition to any surrogate endpoints, whenever possible.[12]

An important aspect of evaluating coronary protection in randomized clinical trials is the variability of effect observed even within a drug class.[7,8,14,15] Drugs with similar pharmacologic profiles, such as different calcium antagonists, may have very different actions[14,15]; the same may be true for β blockers as well.[7,8,16] Consequently, findings of a study evaluating one agent from a class of compounds cannot be extrapolated to the entire class.

To date, preventive effects have been adequately demonstrated in clinical trials for several interventions (Table I). Data indicate that dietary changes in patients with definite hypercholesterolemia reduce the risk of CAD.[17] Although there is a paucity of data from clinical trials on smoking cessation, data from observational studies indicate a positive effect of smoking cessation, in both primary and secondary prevention of CAD.[18] Compliance with a change in life-style, such as dietary modification or smoking cessation, is more difficult to ensure, however, than is compliance with drug therapy.

Some β blockers have been demonstrated to be effective for both primary and secondary prevention of sudden death and MI (Figure 1).[7,8,19] The role of aspirin in secondary prevention is important, although its role in primary prevention has not been well-defined.[20,21] Evidence to date does not support the use of aspirin on a broad scale for primary prevention, at least not in low risk patients.

IMPORTANCE OF SUDDEN CARDIAC DEATH

The high mortality rate from CAD in hypertensive subjects can be reduced substantially only if the risk of sudden coronary deaths can be reduced.[22,23] Therefore, preventive measures should aim at reducing the risk for sudden death, especially in patients with increased risk.

There are 3 important triggering or precipitating factors for ventricular fibrillation and sudden death: ischemia, high sympathetic tone, and low vagal tone.[16,24–29] Increasing vagal tone is protective because it increases electrical stability of the heart. During psychosocial stress, the defense reaction is activated and leads to an increase in sympathetic tone and a decrease in vagal tone. This will decrease the electrical stability of the heart and thus increase the risk of ventricular fibrillation and sudden death.[16,24–32]

The risk of ventricular fibrillation and sudden death may possibly be decreased by reducing ischemia and sympathetic tone and increasing vagal tone. This might be achieved by simultaneously blocking cardiac β_1 receptors and also brain β_1 receptors that control cardiac vagal tone and

electrical stability of the heart. From a theoretical standpoint, one might speculate that relatively lipophilic β blockers that easily pass the blood–brain barrier would more readily confer this than hydrophilic β blockers that only pass the blood–brain barrier to a minor degree.[16,30–32]

Results from animal experiments: Evidence that some β blockers reduce the risk of ventricular fibrillation and sudden death in animals subjected to acute myocardial ischemia is now accumulating.[30–34] The results from animal experiments are of considerable interest and clinical relevance, since they seem to corroborate some observations made in randomized clinical trials.

One early study used a dog model in which animals were pretreated with different doses of atenolol.[33] Two other studies used a pig model and demonstrated that the combination of psychosocial stress caused by restraint in an unfamiliar environment when associated with acute coronary occlusion is very prone to cause ventricular fibrillation.[30,31] Dellsperger and colleagues[34] used dogs in another study in which hypertension leading to left ventricular hypertrophy was induced by unilateral nephrectomy followed by partial occlusion of the remaining renal artery. Åblad and colleagues[32] have advanced our understanding further by a more detailed assessment of cardiac vagal control in a rabbit model in which the autonomic disturbance was provoked by chloralose anesthesia.

All 5 studies indicate that β_1 blockade makes an important contribution to a decrease in the risk of ventricular fibrillation and sudden death. The data published by Skinner,[30] and Parker and coworkers,[31] and Åblad and coworkers[32] also indicate an important role for β_1 receptors located in the brain. The reasons for the reported variations of the antifibrillatory effectiveness of different β blockers are not fully understood[35] but may involve differences in a combination of factors, such as degree of myocardial ischemia and the prevailing sympathetic and vagal activation of the heart as related to dose and the duration of exposure to the given β blocker.

COMMENTS ON HYPERTENSION IN THE ELDERLY

Several large-scale, randomized, double-blind, placebo-controlled studies have been published on the effect of antihypertensive treatment in the elderly,[36–40] and several of these trials have been recently published, the briefly summarized results of which follow. The European Working Party on High Blood Pressure in the Elderly (EWPHE) and the Systolic Hypertension in the Elderly Program (SHEP) studies both compared placebo with thiazide diuretic treatment as baseline therapy. Neither of these studies showed a significant effect on total mortality (EWPHE: −9% and SHEP −13%, differences not significant) or sudden death.

A common misconception is that the EWPHE study showed a significant reduction in coronary events. In the EWPHE study, however, a positive effect of the active treatment was demonstrated mainly on pressure-related complications such as heart failure and stroke. Further, data from the intention-to-treat analysis are only available for fatal events, and cause-specific data for coronary mortality have not yet been published from this analysis.

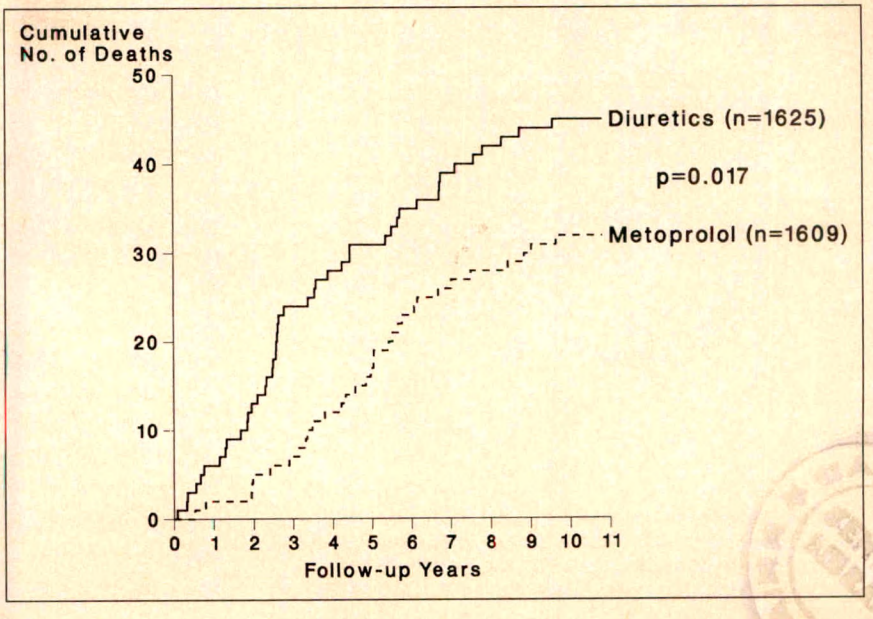


FIGURE 1. Line graph showing cumulative numbers for sudden cardiovascular deaths in the 2 randomization groups in the Metoprolol Atherosclerosis Prevention in Hypertensives (MAPHY) study. The p value refers to the difference in risk between the 2 randomization groups during the entire study period. (Reprinted with permission from *Am J Hypertens.*[19])

TABLE II Sudden Death in the 2 Randomized Groups in the Systolic Hypertension in the Elderly Program (SHEP) Study

Time*	Diuretic (n = 2,365)	Placebo (n = 2,371)
<1 hour	23	23
<24 hours	44	47

*After onset of symptoms.
Adapted from *JAMA*.[38]

The results from the SHEP study, in addition to an effect on stroke of a low-dose diuretic, also showed a significant reduction in the pooled incidence of fatal and nonfatal coronary events. An analysis of sudden cardiac death in the SHEP study, however, showed that 67% of coronary deaths were sudden, without any difference between the 2 treatment groups (Table II). For statistical reasons, it is evidently very difficult to show a significant effect on total or coronary mortality if the treatment does not reduce the risk of sudden death.[22]

The study published by Coope and Warrender[37] compared placebo with atenolol as first-line treatment in elderly hypertensive patients. The results showed a significant reduction of active treatment in stroke, but incidence of coronary events and total mortality was unaffected by treatment (relative risk for coronary events was 1.03, and for total mortality, 0.97).

The Swedish Trial in Old Patients with Hypertension study, in which several different β blockers were part of the first-line treatment, showed a statistically significant effect on total mortality (−43%, p = 0.0079; 95% confidence interval 0.37–0.87) and concomitantly a favorable trend on sudden death.[39] Because of its relatively small size (approximately 200 patients on each β blocker), results were not published separately for each β blocker. No significant reduction in the pooled incidence of fatal and nonfatal coronary events was recorded (relative risk, 0.87; 95% confidence interval 0.49–1.56).

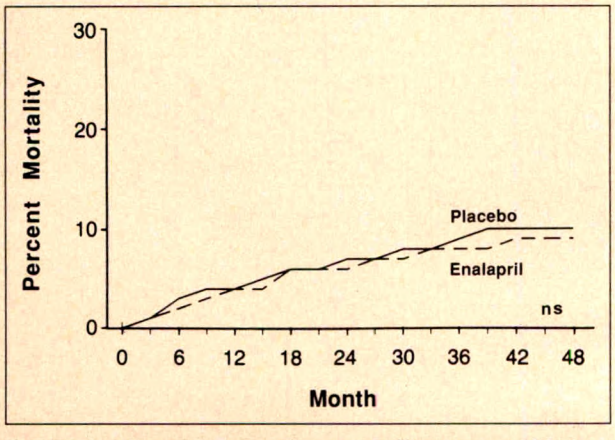


FIGURE 2. Effect of enalapril on mortality presumed to be due to an arrhythmia (sudden death) in the Studies of Left Ventricular Dysfunction (SOLVD). ns = difference not significant. (Reprinted with permission from *N Engl J Med*.[44])

The British Medical Research Council study in older adults compared placebo, thiazide diuretic treatment, and atenolol. In the diuretic group favorable data were seen both for stroke and coronary events, although total mortality and sudden death were unaffected by treatment. An unexpected result was a more favorable outcome for total mortality and coronary events with diuretics compared with atenolol. Thus, these data on the comparison of diuretics and atenolol seem to corroborate the results of the atenolol arm of the Heart Attack Primary Prevention in Hypertension Trial.[7,8,41] To elucidate the reasons why atenolol did not reduce total mortality, sudden death, or other coronary events in any of the 3 trials performed will require further study.

COMMENTS ON ACE INHIBITORS AND CALCIUM ANTAGONISTS

During the last several years, an astonishing increase in the use of angiotensin-converting enzyme (ACE) inhibitors and calcium antagonists has been seen both in patients with hypertension and in patients after MI. It is interesting, therefore, to evaluate critically what data from randomized clinical trials show for these agents. Clinical trials have not yet produced long-term prognostic data on the effects of ACE inhibitors, calcium antagonists, or α blockers on cardiovascular complications and sudden death in hypertensive patients.[6] Long-term prognostic studies with ACE inhibitors in hypertensive patients are urgently needed. One such study is underway.[42]

Several placebo-controlled studies with enalapril have been published on patients with moderate-to-severe congestive heart failure: the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS I),[43] and the Studies of Left Ventricular Dysfunction (SOLVD).[44] In both trials the benefit of treatment was evident in deaths from progressive heart failure but there was no effect on sudden deaths (Figure 2). In the SOLVD trial the benefit was conferred on those with very low ejection fractions (<30%). In another study enalapril was compared with hydralazine–isosorbide dinitrate in patients also with chronic congestive heart failure.[45] The study did not include a placebo group. Since hydralazine may increase the risk of sudden death, results on this endpoint are difficult to judge from this study.

The results from the first secondary preventive placebo-controlled study with an ACE inhibitor (enalapril) in patients with MI have recently been presented.[46] The study was performed in 103 Scandinavian centers with 3,044 patients randomized to enalapril and 3,046 to placebo. Intravenous enalaprilat (the active metabolite of enalapril) was given during the acute phase of an MI followed by 6 months of double-blind oral treatment (20 mg daily). During this follow-up, 598 patients died. The study was stopped prematurely, mainly because of a negative trend in patients randomized to the ACE inhibitor.

There was an equal number of deaths in the 2 groups during the first 5 days after randomization, but thereafter the curves started to diverge and the results showed a nonsignificant slightly higher relative risk with enalapril compared with placebo (relative risk 1.10; 95% confidence interval 0.93–1.30; $p = 0.28$). The results from this study contrast with the beneficial effect shown on total mortality and sudden death with a β blocker using a very similar study design (intravenous followed by long-term oral treatment in patients with MI).[47] Although animal data indicate that ACE inhibition (captopril) may have an antiatherogenic effect,[48] results regarding sudden death from randomized clinical trials have not been encouraging.

Animal data indicate that calcium antagonists also may have an antiatherogenic effect, especially with regard to the development of new lesions.[49] Calcium antagonists have also been extensively studied in post-MI patients. A recent review concluded that the results were disappointing, since pooled data actually showed a trend toward increased mortality with the calcium antagonists compared with placebo (Table III).[50] There is some evidence, however, that the effect of verapamil in post-MI patients might differ from that of calcium antagonists of the dihydropyridine type,[51,52] although there are no data to indicate that verapamil significantly affects total mortality or sudden death.

The available, large-scale, randomized secondary preventive trials with ACE inhibitors and calcium antagonists indicate that results with regard to sudden death have been disappointing.

COMBINATION TREATMENT AND OTHER ISSUES

A large number of patients with mild-to-moderate hypertension are not well-controlled on a low-to-moderate dose of a single drug. The dose–response curves for antihypertensive drugs are rather flat and therefore the strategy of combining drugs rather than increasing the doses seems to be an advantage for blood pressure control and for quality of life, and possibly for coronary protection. The same considerations must be taken into account in combining drugs as when choosing the initial drug, i.e., what impact the combination will have on total mortality and on the risk of coronary events occurring, and what effect it will have on quality of life. Present data indicate improved quality of life with ACE inhibitors and different cardioselective β blockers.[53] Nonselective β blockers such as propranolol, however, do not seem to be as well tolerated (Figure 3).[54,55] Further studies are needed to define the way in which different drugs and drug combinations affect both the underlying atherosclerotic disease and mechanisms that may influence precipitating factors for ventricular fibrillation and sudden death, as well as life satisfaction and quality of life.

TABLE III Pooled Results from Post-Myocardial Infarction Patients with Calcium Antagonists of the Dihydropyridine Type

Endpoint	Calcium Antagonists (n = 4,731)	Placebo (n = 4,733)	% Difference
Reinfarction	124	111	+11
Total mortality	365	330	+4

Adapted from *Am J Cardiol.*[52]

CONCLUSION

Coronary protection can be defined as the prevention or delay of sudden cardiac death and MI without negatively affecting noncardiovascular mortality. The aggressive pharmacologic approach to coronary protection pursued in the United

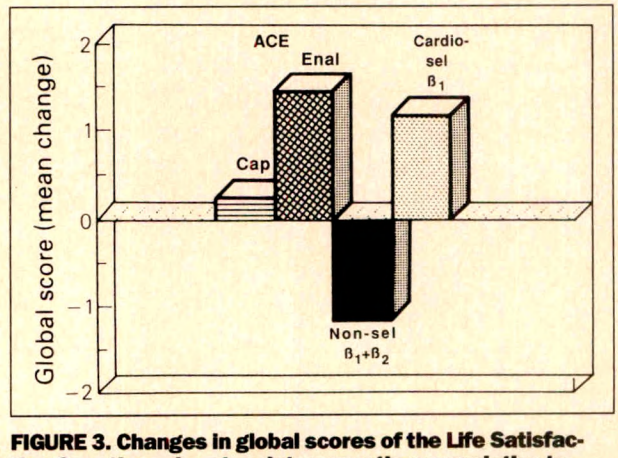


FIGURE 3. Changes in global scores of the Life Satisfaction Questionnaire at maintenance therapy relative to baseline. ACE = angiotensin converting enzyme inhibitors; Cap = captopril; Enal = enalapril; Cardiosel = cardioselective (atenolol); Non-sel = nonselective (propranolol). (Reprinted with permission from *J Hum Hypertens.*[54])

States contrasts with the more conservative approach taken in Europe. In common with their more conservative view toward the treatment of mild hypercholesterolemia, European experts in the hypertensive field have expressed disagreements with the position of experts in the United States on the use of antihypertensive drugs in patients with mild hypertension.

On what evidence, then, should we base our treatment decisions and make the best choice among treatment alternatives? The clinical trial is a key research activity with the potential to improve the quality of health care by careful comparison of alternative treatments. Present data indicate an important role for some β blockers in secondary prevention after MI and also for primary prevention in men with mild-to-moderate hypertension. Data available from post-MI patients also indicate a very important clinical role for β blockade in patients with diabetes, a group with a high risk of sudden death.[7,8,56] Other data from the post-MI situation indicate a similar benefit in Blacks and Caucasians, and in both males and females.[57,58]

Adding aspirin to β blockade will further reduce the risk for coronary events in patients after an MI.[21] Evidence to date, however, does not support the use of aspirin on a broad scale for primary prevention, at least not in low risk patients. In addition to the choice of drug used, risk reduction is probably also dependent on improved detection and the effective management of concomitant risk factors for CAD, especially smoking cessation.

Clinical trials to date have not yet produced long-term primary prevention data on the effects of ACE inhibitors, calcium antagonists, or α blockers on cardiovascular complications and sudden death in hypertensive patients. Large-scale secondary preventive studies presently available on ACE inhibitors and calcium antagonists indicate that the results with regard to sudden death have been disappointing, although results on the prevention of death from progressive heart failure are important.

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